PRODUCT MONOGRAPH

PrRISPERDAL CONSTA®

risperidone powder for Injectable Prolonged-Release Suspension
12.5 mg, 25 mg, 37.5 mg and 50 mg

Antipsychotic Agent

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9
www.janssen.com/canada

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Nonmedicinal Ingredients
Intramuscular injection	Powder for Injectable Prolonged-Release Suspension 12.5 mg, 25 mg, 37.5 mg and 50 mg	Citric acid anhydrous, disodium hydrogen phosphate dihydrate, polylactide-co-glycolide (PLG), polysorbate 20, sodium carboxymethylcellulose, sodium chloride, sodium hydroxide, water for injection.

INDICATIONS AND CLINICAL USE

ADULTS

Schizophrenia and Related Disorders

RISPERDAL CONSTA® (risperidone) powder for injectable prolonged-release suspension is indicated for the management of the manifestations of schizophrenia and related psychotic disorders. RISPERDAL CONSTA® was found to improve both positive and negative symptoms of schizophrenia.

The efficacy of RISPERDAL CONSTA® is based in part on a 12-week, placebo-controlled trial in schizophrenic inpatients or outpatients, along with extrapolation from the established efficacy of oral RISPERDAL® in this population.

The effectiveness of RISPERDAL CONSTA® in longer-term use, that is, more than 12 weeks, has not been systematically evaluated in controlled trials. However, oral RISPERDAL® has been shown to be effective in maintaining clinical improvement during long-term therapy (1 year). Patients should be periodically reassessed to determine the need for continued treatment (see **DOSAGE AND ADMINISTRATION**).

Bipolar Disorder
RISPERDAL CONSTA® is indicated as monotherapy maintenance treatment in patients with bipolar I disorder, who have previously responded to oral antipsychotics or other anti-manic treatment, to delay occurrence of manic episodes.

For patients who have never taken oral risperidone, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with RISPERDAL CONSTA®.

Geriatrics (>65 years of age):
See **WARNINGS AND PRECAUTIONS — Serious Warnings and Precautions Box** and **Special Populations**.

Pediatrics (<18 years of age):
No data available and its use is not recommended. See **WARNINGS AND PRECAUTIONS — Special Populations**.

CONTRAINDICATIONS

RISPERDAL CONSTA® is contraindicated in patients who are hypersensitive to risperidone, paliperidone, or to any other ingredient in the formulation or component of the container (see **WARNINGS AND PRECAUTIONS**, **Immune**, Hypersensitivity, and **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**). For a complete listing of ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia
Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature (see WARNINGS AND PRECAUTIONS — Special Populations, Use in Geriatric Patients with Dementia).

General

Administration

RISPERDAL CONSTA® should be injected into the gluteal or deltoid muscle, and care must be taken to avoid inadvertent injection of RISPERDAL CONSTA® into a blood vessel (see **DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS — Post-Market Adverse Drug Reactions** [retinal artery occlusion]).

QT Interval

As with other antipsychotics, caution should be exercised when RISPERDAL CONSTA® is prescribed in patients with a history of cardiac arrhythmias, in patients with congenital long QT syndrome, and in concomitant use with drugs known to prolong the QT interval.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when prescribing RISPERDAL CONSTA® for patients who will be experiencing conditions which may contribute to an elevation or reduction of core body temperature, e.g., exercising strenuously, exposure to extreme heat or cold, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including RISPERDAL CONSTA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Carcinogenesis and Mutagenesis

Osteodystrophy and Tumours in Animals

RISPERDAL CONSTA® produced osteodystrophy in male and female rats in a 1-year toxicity study and a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks.

RISPERDAL CONSTA® produced renal tubular tumours (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. In addition, RISPERDAL CONSTA® produced an increase in a marker of cellular proliferation in renal tissue in males in the 1-year toxicity study and in renal tumour-bearing males in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. (Cellular proliferation was not measured at the low dose or in females in either study.)

The effect dose for osteodystrophy and the tumour findings is 8 times the IM maximum recommended human dose (MRHD) (50 mg) on a mg/m^2 basis and is associated with a plasma exposure (AUC) 2 times the expected plasma exposure (AUC) at the IM MRHD. The no-effect dose for these findings was 5 mg/kg (equal to the IM MRHD on a mg/m^2 basis). Plasma

exposure (AUC) at the no-effect dose was one-third the expected plasma exposure (AUC) at the IM MRHD.

Neither the renal or adrenal tumours, nor osteodystrophy, was seen in studies of orally administered risperidone. Osteodystrophy was not observed in dogs at doses up to 14 times (based on AUC) the IM MRHD in a 1-year toxicity study.

The renal tubular and adrenomedullary tumours in male rats and other tumour findings are described in more detail under **WARNINGS AND PRECAUTIONS** — Carcinogenesis, Mutagenesis, Impairment of Fertility.
The relevance of these findings to human risk is unknown.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis — Oral
Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the oral maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis, or 0.2, 0.75, and 3 times the oral MRHD (mice) or 0.4, 1.5, and 6 times the oral MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There was a significant increase in pituitary gland adenomas in female mice at doses 0.75 and 3 times the oral MRHD on a mg/m^2 basis. There was a significant increase in endocrine pancreatic adenomas in male rats at doses 1.5 and 6 times the oral MRHD on a mg/m^2 basis. Mammary gland adenocarcinomas were significantly increased in female mice at all doses tested (0.2, 0.75, and 3 times the oral MRHD on a mg/m^2 basis), in female rats at all doses tested (0.4, 1.5, and 6 times the oral MRHD on a mg/m^2 basis), and in male rats at a dose 6 times the oral MRHD on a mg/m^2 basis.

Carcinogenesis — IM
RISPERDAL CONSTA® was evaluated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with IM injections of either 5 mg/kg or 40 mg/kg of risperidone. These doses are 1 and 8 times the MRHD (50 mg) on a mg/m^2 basis. A control group received injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres. There was a significant increase in pituitary gland adenomas, endocrine pancreas adenomas, and adrenomedullary pheochromocytomas at 8 times the IM MRHD on a mg/m^2 basis. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 8 times the IM MRHD on a mg/m^2 basis). A significant increase in renal tubular tumours (adenomas, adenocarcinomas) was observed in male rats at 8 times the IM MRHD on a mg/m^2 basis. Plasma exposures (AUC) in rats were 0.3 and 2 times (at 5 and 40 mg/kg, respectively) the expected plasma exposure (AUC) at the IM MRHD.

Dopamine D_2 receptor antagonists have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies of oral risperidone; however, measurements taken during subchronic toxicity studies showed that oral risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the oral carcinogenicity studies. Serum prolactin levels increased in a dose-dependent manner up

to 6- and 1.5-fold in male and female rats, respectively, at the end of the 24-month treatment with RISPERDAL CONSTA® every 2 weeks. Increases in the incidence of pituitary gland, endocrine pancreas, and mammary gland neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and may be prolactin-mediated.

The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unknown (see **WARNINGS AND PRECAUTIONS** — Hyperprolactinemia).

Mutagenesis
No evidence of mutagenic potential for oral risperidone was found in the in vitro Ames reverse mutation test, in vitro mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo oral micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the in vitro chromosomal aberration test in human lymphocytes or in Chinese hamster cells.

In addition, no evidence of mutagenic potential was found in the in vitro Ames reverse mutation test for RISPERDAL CONSTA®.

Impairment of Fertility
Oral risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two mating and fertility studies and a multigenerational study) at doses 0.1 to 3 times the oral maximum recommended human dose (MRHD) (16 mg/day) on a mg/m^2 basis. The effect appeared to be in females, since impaired mating behaviour was not noted in the mating and fertility study in which males only were treated. In a subchronic study in Beagle dogs in which oral risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the oral MRHD on a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm values partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

No mating and fertility studies were conducted with RISPERDAL CONSTA®.

Cardiovascular
RISPERDAL CONSTA® may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.8% (12/1499) of patients treated with RISPERDAL CONSTA® in repeated-dose studies. Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone and antihypertensive treatment.

RISPERDAL CONSTA® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of 202 schizophrenic patients treated with 25 mg or 50 mg RISPERDAL CONSTA® and 98 schizophrenic patients treated with placebo in a double-blind, placebo-controlled trial were evaluated. Compared with placebo, there were no statistically

significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL CONSTA®.

The electrocardiograms of 227 patients were evaluated in the 24-month double-blind, placebo-controlled treatment period of a trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder. There were no clinically relevant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL CONSTA® compared to placebo.

RISPERDAL CONSTA® should be used with caution in the elderly and patients with renal or hepatic impairment, as well as those with cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, cerebrovascular disease, conduction abnormalities), and conditions such as dehydration and hypovolemia. Special care should be taken to avoid hypotension in patients with a history of cerebrovascular insufficiency or ischemic heart disease, and in patients taking medications to lower blood pressure. Monitoring of cardiovascular signs should be considered in all such patients.

Endocrine and Metabolism

Hyperglycemia and Diabetes Mellitus

As with some other antipsychotics, hyperglycemia, diabetes mellitus, and exacerbation of pre-existing diabetes, in some cases serious and associated with ketoacidosis or hyperosmolar coma or death, have been reported during the use of RISPERDAL® (see **ADVERSE REACTIONS — Post-Market Adverse Drug Reactions**).

Diabetic ketoacidosis (DKA) has occurred in patients treated with antipsychotics with no reported history of hyperglycemia. Appropriate clinical monitoring of patients treated with antipsychotics is advisable in accordance with utilized antipsychotic guidelines.

Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Any patient treated with atypical antipsychotics, including RISPERDAL®, should be monitored for symptoms of hyperglycemia and diabetes mellitus including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia and diabetes mellitus during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the

suspect drug. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Dyslipidemia
Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Hyperprolactinemia
As with other atypical antipsychotics that antagonize dopamine D2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, RISPERDAL CONSTA® should only be administered to patients with previously detected breast cancer if the benefits outweigh the potential risks. Caution should also be exercised when considering RISPERDAL CONSTA® treatment in patients with pituitary tumours. Possible manifestations associated with elevated prolactin levels are galactorrhoea, nonpuerperal lactation, amenorrhea, gynecomastia, abnormal sexual function, ejaculation failure, decreased libido, and impotence. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

As is common with compounds that increase prolactin release, increases in pituitary gland, mammary gland, and adrenal medullary neoplasia, as well as endocrine pancreatic islet cell hyperplasia and/or neoplasia, were observed with oral RISPERDAL® and RISPERDAL CONSTA® in carcinogenicity studies conducted in mice and rats (see ***Product Monograph Part II:*** **TOXICOLOGY — Carcinogenicity**). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans. The available evidence is considered too limited to be conclusive at this time.

Weight Gain
Significant weight gain has been reported in both clinical trials and post-marketing. Monitoring weight gain is advised when RISPERDAL® is being used (see **ADVERSE REACTIONS — Post-Market Adverse Drug Reactions**).

In the 12-week, placebo-controlled study in patients with schizophrenia, 9% of patients treated with RISPERDAL CONSTA® (25 mg or 50 mg) and 6% of placebo-treated patients met a weight gain criterion of >7%. With continued treatment, weight gain (mean: 2.6 kg in the long-term study) has been seen.

In the 24-month, double-blind, placebo-controlled treatment period of the trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder, 11.6% of patients treated with

RISPERDAL CONSTA® compared with 2.8% of patients treated with placebo experienced a weight gain of >7% of body weight at endpoint.

Gastrointestinal

Antiemetic Effect

Consistent with its dopamine antagonistic effects, RISPERDAL CONSTA® may have an antiemetic effect. Such an effect may mask signs of toxicity due to overdosage with other drugs, or may mask symptoms of disease such as brain tumour, intestinal obstruction or Reye's syndrome.

Genitourinary

Priapism

Drugs with alpha-adrenergic-blocking effects have been reported to induce priapism. Priapism has been reported with risperidone during post-marketing surveillance. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic

Leukopenia, Neutropenia, and Agranulocytosis Class Effect

In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including RISPERDAL®. Granulocytopenia and agranulocytosis have also been reported.

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

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 x 10^9/L) should discontinue RISPERDAL® and have their WBC followed until recovery (see **ADVERSE REACTIONS - Post-Market Adverse Drug Reactions)**.

Venous Thromboembolism

Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including RISPERDAL CONSTA®, in case reports and/or observational studies. When prescribing RISPERDAL CONSTA® all potential risk factors for VTE should be identified and preventative measures undertaken.

Hepatic/Biliary/Pancreatic

Use in Patients with Hepatic Impairment

Whereas the pharmacokinetics of oral RISPERDAL® in patients with hepatic impairment were comparable to those in young volunteers, the mean free fraction of risperidone was increased by

about 35%. Although patients with hepatic impairment were not studied with RISPERDAL CONSTA®, it is recommended that patients with any degree of hepatic impairment be carefully titrated on oral RISPERDAL®/RISPERDAL M-TAB® before treatment with RISPERDAL CONSTA® is initiated at a dose of 25 mg. Alternatively, a starting dose of 12.5 mg RISPERDAL CONSTA® may be appropriate (see **DOSAGE AND ADMINISTRATION**).

Immune

Hypersensitivity

There have been very rare spontaneous post-marketing reports of severe hypersensitivity (e.g., anaphylaxis, angioedema, anaphylactic shock) in some patients after injection with RISPERDAL CONSTA®. It is unknown how many of these patients previously tolerated oral risperidone or paliperidone. **However, anaphylactic-type reactions have occurred after injection with RISPERDAL CONSTA® in patients who have previously tolerated oral risperidone or oral paliperidone**. Symptoms of anaphylaxis include skin rash, hives, peripheral edema, swollen eye, tongue and face, hyperhidrosis, dyspnea, and hypotension. Further treatment with RISPERDAL CONSTA® should be discontinued if such symptoms occur. Patients with hypersensitivity to oral risperidone, paliperidone, or to any other ingredient of the formulation or component of the container, should not be treated with RISPERDAL CONSTA® (see **CONTRAINDICATIONS**). Caution should also be exercised in patients who have had serious allergic reactions to other medications. Prior to initiating treatment with RISPERDAL CONSTA®, tolerability with oral risperidone should be established (see **DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**). For a complete listing of ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Neurologic

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including RISPERDAL®.

Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular blood pressure, tachycardia, cardiac arrhythmias, and diaphoresis). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of all antipsychotic drugs including RISPERDAL CONSTA®, and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general

agreement about specific pharmacological treatment regimens for uncomplicated NMS. After the last administration of RISPERDAL CONSTA®, plasma levels of risperidone are present for up to a minimum of 6 weeks.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrence of NMS has been reported.

Tardive Dyskinesia (TD)

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with conventional antipsychotic drugs. Although TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which patients are likely to develop TD. It has been suggested that the occurrence of parkinsonian side effects is a predictor for the development of TD. In clinical studies with oral RISPERDAL®, the observed incidence of drug-induced parkinsonism was lower with RISPERDAL® than with haloperidol. In the optimal clinical dose range, the difference between risperidone and haloperidol was significant. The risk of developing TD may be less with RISPERDAL® and RISPERDAL CONSTA®.

The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although less commonly, after relatively brief periods of treatment at low doses. There is no known treatment for established cases of TD. The syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. However, antipsychotic drug treatment itself may suppress the signs and symptoms of TD, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown.

In view of these considerations, RISPERDAL CONSTA® should be prescribed in a manner that is most likely to minimize the risk of TD. As with any antipsychotic drug, RISPERDAL CONSTA® should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of TD develop during treatment with RISPERDAL CONSTA®, withdrawal of the drug should be considered. However, some patients may require treatment with RISPERDAL CONSTA® despite the presence of the syndrome.

Potential for Cognitive and Motor Impairment

Somnolence was reported by 5% of patients treated with RISPERDAL CONSTA® in repeated-dose trials. Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with RISPERDAL CONSTA® does not affect them adversely.

Seizures

During premarketing testing, seizures occurred in 0.3% (5/1499) of patients treated with RISPERDAL CONSTA®. Therefore, RISPERDAL CONSTA® should be used cautiously in patients with a history of seizures.

Use in Patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB)

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) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Ophthalmologic

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including RISPERDAL CONSTA® (see **ADVERSE REACTIONS — Post-Market Adverse Drug Reactions**).

This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions. IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Psychiatric

Suicide

The possibility of suicide or attempted suicide is inherent in psychosis and bipolar disorder, and thus, close supervision and appropriate clinical management of high-risk patients should accompany drug therapy. RISPERDAL CONSTA® is to be administered by a healthcare professional (see **DOSAGE AND ADMINISTRATION**); therefore, suicide due to an overdose is unlikely.

Renal

Use in Patients with Renal Impairment

The pharmacokinetics of oral RISPERDAL® were significantly altered in patients with renal disease. In a study with oral risperidone in patients with moderate to severe renal disease, clearance of risperidone and its active metabolite 9-hydroxyrisperidone combined decreased by 60% compared to young healthy subjects (see **ACTION AND CLINICAL PHARMACOLOGY — Special Populations and Conditions**). Although patients with renal impairment were not studied with RISPERDAL CONSTA®, it is recommended that patients with any degree of renal impairment be carefully titrated on oral RISPERDAL®/RISPERDAL M-

TAB® with lower starting doses and lower maximal doses, before treatment with RISPERDAL CONSTA® is initiated at a dose of 25 mg. Alternatively, a starting dose of 12.5 mg RISPERDAL CONSTA® may be appropriate. It may also be useful to monitor renal function in these patients (see **DOSAGE AND ADMINISTRATION**).

Special Populations

Pregnant Women:

Teratogenic Effects

The safety of RISPERDAL CONSTA® during pregnancy has not been established. No clinical studies have been conducted with RISPERDAL CONSTA®. 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. Compared to no antipsychotic exposure, the relative risk of congenital malformations with risperidone, after adjusting for confounder variables available in the database, was statistically significant (relative risk=1.26, 95% CI: 1.02-1.56). No biological mechanism has been identified to explain these findings and teratogenic effects have not been observed in non clinical studies. Based on the findings of this single observational study, a causal relationship between *in utero* exposure to risperidone and congenital malformations has not been established.

In animal studies, risperidone did not show direct reproductive toxicity. However, due to its prolactin-elevating and CNS-depressant activities, reproductive performance and pup survival were adversely affected in rats. Risperidone was not teratogenic in either rats or rabbits. The microspheres are hydrolyzed to the endogenous components of lactic acid and hydroxyacetic acid, which are not teratogenic.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to risperidone therapy is unknown (see ***Product Monograph Part II*: TOXICOLOGY - Reproductive and Developmental Toxicology**).

Non-Teratogenic Effects

Neonates exposed to antipsychotic drugs (including RISPERDAL®) during the third trimester of pregnancy are at risk of extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

RISPERDAL CONSTA® should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

Nursing Women: Risperidone appeared in the milk of lactating dogs. The concentration of risperidone was similar in milk and plasma, while that of 9-hydroxyrisperidone was higher in

milk than in plasma. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast milk.

Nursing should not be undertaken while a patient is receiving RISPERDAL CONSTA® and for at least 12 weeks after the last injection.

Pediatrics (<18 years of age): The safety and efficacy of RISPERDAL CONSTA® in children under the age of 18 have not been established and its use is not recommended.

Weight gain has been observed with atypical antipsychotic use in pediatric and adolescent patient populations. Independent of any drug-specific effects, weight gain can be associated with adverse changes in other metabolic parameters (e.g., glucose and lipid metabolism). Abnormal childhood weight and metabolic status can have adverse effects on cardiovascular outcomes in adulthood. Weight gain and adverse effects on other metabolic parameters associated with typical antipsychotics can be more frequent or more severe in pediatric and adolescent patients than in the adult patients.

The long-term safety, including cardiometabolic effects and effects on growth, maturation and behavioural development in patients under 18 years of age has not been systematically evaluated.
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Geriatrics (>65 years of age): Geriatric patients generally have decreased renal, hepatic and cardiac function, and an increased tendency to postural hypotension. Therefore, lower starting doses, lower rates of dose adjustment and lower maximal doses are recommended in these patients.

Risperidone is substantially excreted by the kidneys. Thus, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, caution should be taken in dose selection and titration. It may also be useful to monitor renal function in these patients (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY — Pharmacokinetics**).

In an open-label study, 57 clinically stable elderly patients with schizophrenia (≥ 65 years old) received RISPERDAL CONSTA® every 2 weeks for up to 12 months. In general, no differences in the tolerability of RISPERDAL CONSTA® were observed between otherwise healthy elderly and nonelderly patients. RISPERDAL CONSTA® has not been studied in elderly patients with bipolar disorder. Dosing recommendations for otherwise healthy elderly patients are the same as for nonelderly patients. Because elderly patients exhibit a greater tendency to orthostatic hypotension than nonelderly patients, elderly patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). In addition, monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is of concern (see **WARNINGS AND PRECAUTIONS — Cardiovascular**, **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Use in Geriatric Patients with Dementia

Overall Mortality

Elderly patients with dementia treated with atypical antipsychotic drugs have an increased mortality compared to placebo in a meta-analysis of 13 controlled trials of various atypical antipsychotic drugs. In six 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.

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), furosemide alone (4.1%; mean age 80 years, range 67—90) or placebo without furosemide (2.9%; mean age 88 years, range 71—100). 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 has been 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 (CVAEs) in Elderly Patients with Dementia

In placebo-controlled trials in elderly patients with dementia, there was a significantly higher incidence of cerebrovascular adverse events (stroke and transient ischemic attacks) including fatalities in patients (mean age 85 years; range 73—97) treated with oral RISPERDAL® compared to patients receiving placebo. There is insufficient information to determine whether CVAEs in elderly patients with dementia are associated specifically with RISPERDAL® or other antipsychotic agents.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL CONSTA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The prescriber should be aware that the numbers in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Schizophrenia

The safety of RISPERDAL CONSTA® was evaluated from a clinical trial database consisting of 1499 patients exposed to one or more doses of RISPERDAL CONSTA® for the treatment of schizophrenia. Of these 1499 patients, 332 were patients who received RISPERDAL CONSTA® while participating in a 12-week, double-blind, placebo-controlled trial. A total of 202 of the 332 were patients with schizophrenia who received 25 mg or 50 mg RISPERDAL CONSTA®. The conditions and duration of treatment with RISPERDAL CONSTA® in the other clinical trials varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 4 years) exposures.

Adverse findings were assessed by spontaneous reports of adverse events, laboratory tests, vital signs, body weight, and ECGs. Adverse events were classified using the World Health Organization preferred terms. Treatment-emergent adverse events were defined as those events with an onset between the first dose and 49 days after the last dose.

Adverse Events Associated with Discontinuation of Treatment

RISPERDAL CONSTA® is generally well tolerated at doses of 12.5 mg to 50 mg. In the 12-week, placebo-controlled trial in patients with schizophrenia who received 25 mg or 50 mg, the incidence of patients who discontinued treatment due to an adverse event was lower with RISPERDAL CONSTA® (11%; 22/202 patients) than with placebo (13%; 13/98 patients). The more common adverse events causing discontinuation included: psychiatric (17% vs. 11% placebo): primarily psychosis, hallucination, agitation, suicide attempt, and anxiety; neurological (1.4% vs. 1% placebo): primarily hyperkinesia. No adverse events leading to discontinuation were found to be unexpected nor were considered to be clinically relevant to RISPERDAL CONSTA®.

Commonly Observed Adverse Events in the Controlled Clinical Trial

Table 1.1 enumerates adverse events that occurred at an incidence of 2% or more, and were at least as frequent among schizophrenic patients treated with 25 mg or 50 mg RISPERDAL CONSTA® as patients treated with placebo in the 12-week, placebo-controlled trial. This table shows the percentage of patients in each dose group who spontaneously reported at least one episode of an event at some time during double-blind treatment. All patients were titrated to a dose of 4 mg oral RISPERDAL® during a one-week run-in period. Patients who received RISPERDAL CONSTA® were given doses of oral RISPERDAL® (2 mg for patients in the 25 mg group, and 4 mg for patients in the 50 mg group) during the 3 weeks after the first injection to provide therapeutic levels until the main release phase of risperidone from the injection site had begun. Patients who received placebo injections were given placebo tablets.

Serious Adverse Events

In the 12-week, placebo-controlled trial, the most frequently reported serious adverse events during the double-blind period among schizophrenic patients were psychosis, hallucination, agitation, suicide attempt, and anxiety. No serious adverse events were found to be unexpected nor were considered to be clinically relevant to RISPERDAL CONSTA®.

Table 1.1: Treatment-Emergent Adverse Events Reported by ≥ 2% of Patients with Schizophrenia Treated with RISPERDAL CONSTA® and Equal or Greater than Placebo -in a 12-Week, Double-Blind, Placebo-Controlled Clinical Trial

	Percentage of Patients Reporting Event		
		RISPERDAL CONSTA®	
WHO Body System Disorder/Preferred Term	Placebo (n=98)	25 mg (n=99)	50 mg (n=103)
Psychiatric			
Insomnia	14	16	13
Hallucination	5	7	6
Somnolence	3	5	6
Suicide attempt	3	1	4
Abnormal thinking	2	0	3
Abnormal dreaming	0	2	0
Central & peripheral nervous system			
Headache	12	15	22
Dizziness	6	8	11
Akathisia	4	2	9
Parkinsonism[a]	3	4	10
Tremor	0	0	3
Hypoesthesia	0	2	0
Gastrointestinal			
Dyspepsia	2	7	7
Constipation	1	5	7
Mouth dry	1	0	7
Toothache	0	1	3
Saliva increased	1	6	2
Tooth disorder	0	4	2
Diarrhea	3	5	1
Body as a whole — general			
Fatigue	0	3	7
Pain	4	10	3
Peripheral edema	1	2	3
Leg pain	1	4	1
Fever	0	2	1
Syncope	0	2	0
Respiratory system			
Rhinitis	8	14	4
Coughing	4	5	2
Sinusitis	0	3	1
Upper respiratory tract infection	1	2	0
Metabolic & nutritional			
Weight increase	2	5	4
Weight decrease	1	4	1
Cardiovascular			
Hypertension	2	3	3
Hearing & vestibular			
Ear disorder (NOS)[b]	0	0	3
Vision			
Vision abnormal	0	2	3
Skin & appendage			
Acne	0	2	2
Skin dry	0	2	0
Musculoskeletal			
Myalgia	1	4	2

[a] Includes adverse events of bradykinesia, extrapyramidal disorder, and hypokinesia.

[b] Not Otherwise Specified

Adverse Reactions During Long-Term Treatment

The long-term safety of RISPERDAL CONSTA® was evaluated in 615 patients with schizophrenia treated up to one year with 25 mg, 50 mg, or 75 mg in an open trial. A total of 400 patients completed the one-year trial. The most frequently reported adverse events (> 10%) for all dose groups combined were anxiety, psychosis, insomnia, depression, headache, hyperkinesia and rhinitis.

Less Common Clinical Trial Adverse Drug Reactions (≤ 1%)

During its premarketing assessment, RISPERDAL CONSTA® was administered to 1499 patients in multiple-dose studies. The conditions and duration of exposure to RISPERDAL CONSTA® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term and long-term exposure studies. In all studies, untoward events associated with this exposure were obtained by spontaneous report and were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 1499 patients exposed to multiple doses of RISPERDAL CONSTA® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL CONSTA®. All reported events are included except those already listed in Table 1.1, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the reported events occurred during treatment with RISPERDAL CONSTA®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from the placebo-controlled trial appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; and rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: anxiety, psychosis, depression, agitation, nervousness, paranoid reaction, delusion, apathy. *Infrequent:* anorexia, impaired concentration, impotence, emotional lability, manic reaction, decreased libido, increased appetite, amnesia, confusion, euphoria, depersonalization, paroniria, delirium, psychotic depression.

Central and Peripheral Nervous System Disorders

Frequent: hypertonia, dystonia. *Infrequent:* dyskinesia, vertigo, leg cramps, tardive dyskinesia[a], involuntary muscle contractions, paresthesia, abnormal gait, bradykinesia, convulsions, hypokinesia, ataxia, fecal incontinence, oculogyric crisis, tetany, apraxia, dementia, migraine. *Rare:* neuroleptic malignant syndrome.

[a]In the integrated database of multiple-dose studies (1499 patients with schizophrenia or schizoaffective disorder), 9 patients (0.6%) treated with RISPERDAL CONSTA® (all dosages combined) experienced an adverse event of tardive dyskinesia.

Body as a Whole/General Disorders
Frequent: back pain, chest pain, asthenia, edema. *Infrequent:* malaise, choking, hypersensitivity.

Gastrointestinal Disorders
Frequent: nausea, vomiting, abdominal pain. *Infrequent:* gastritis, gastroesophageal reflux, flatulence, hemorrhoids, melena, dysphagia, rectal hemorrhage, stomatitis, colitis, gastric ulcer, gingivitis, irritable bowel syndrome, ulcerative stomatitis.

Respiratory System Disorders
Frequent: dyspnea. *Infrequent:* pneumonia, stridor, hemoptysis. *Rare:* pulmonary edema.

Skin and Appendage Disorders
Frequent: rash. *Infrequent:* eczema, pruritus, erythematous rash, dermatitis, alopecia, seborrhea, photosensitivity reaction, increased sweating.

Metabolic and Nutritional Disorders
Infrequent: hyperuricemia, hyperglycemia, hyperlipemia, hypokalemia, glycosuria, hypercholesterolemia, obesity, dehydration, diabetes mellitus, hyponatremia.

Musculoskeletal System Disorders
Frequent: arthralgia, skeletal pain. *Infrequent:* torticollis, arthrosis, muscle weakness, tendinitis, arthritis, arthropathy.

Heart Rate and Rhythm Disorders
Frequent: tachycardia, electrocardiogram abnormal. *Infrequent:* bradycardia, AV block, palpitation, bundle branch block, conduction disorder, electrocardiogram QT prolonged. *Rare:* T-wave inversion.

Cardiovascular Disorders
Frequent: hypotension. *Infrequent:* postural hypotension.

Urinary System Disorders
Frequent: urinary incontinence. *Infrequent:* hematuria, micturition frequency, renal pain, urinary retention.

Vision Disorders
Infrequent: conjunctivitis, eye pain, abnormal accommodation, photophobia.

Reproductive Disorders, Female
Frequent: amenorrhea. *Infrequent:* nonpuerperal lactation, vaginitis, dysmenorrhea, breast pain, leukorrhea.

Resistance Mechanism Disorders
Infrequent: abscess, infection.

Liver and Biliary System Disorders
Frequent: increased hepatic enzymes. *Infrequent:* hepatomegaly, increased SGPT. *Rare:* bilirubinemia, increased GGT, hepatitis, hepatocellular damage, jaundice, fatty liver, increased SGOT.

Reproductive Disorders, Male
Infrequent: ejaculation failure.

Application Site Disorders
Frequent: injection site pain. *Infrequent:* injection site reaction.

Hearing and Vestibular Disorders
Infrequent: earache, deafness, hearing decreased.

Red Blood Cell Disorders
Frequent: anemia.

White Cell and Resistance Disorders
Infrequent: lymphadenopathy, leukopenia, cervical lymphadenopathy. *Rare:* granulocytopenia, leukocytosis, lymphopenia.

Endocrine Disorders
Infrequent: hyperprolactinemia, gynecomastia, hypothyroidism.

Platelet, Bleeding and Clotting Disorders
Infrequent: purpura, epistaxis. *Rare:* pulmonary embolism, hematoma, thrombocytopenia.

Myo-, Endo-, and Pericardial and Valve Disorders
Infrequent: myocardial ischemia, angina pectoris, myocardial infarction.

Vascular (Extracardiac) Disorders
Infrequent: phlebitis. *Rare:* intermittent claudication, flushing, thrombophlebitis.

Bipolar Disorder
Safety data are presented from a clinical trial assessing the efficacy and safety of RISPERDAL CONSTA® as monotherapy maintenance treatment in patients with bipolar I disorder. Patients who met criteria for a stable response to treatment with RISPERDAL CONSTA® during a 26-week open label stabilization period were randomized into a 24-month double-blind placebo-controlled period in which they received RISPERDAL CONSTA® (n=154) or placebo (n=149) as monotherapy. The majority of patients were treated with the 25 mg dose of RISPERDAL CONSTA® (see ***Product Monograph Part II:*** **CLINICAL TRIALS**).

Safety data are also presented from a clinical trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as adjunctive maintenance treatment in patients with bipolar disorder. In this study, patients who met criteria for stable remission following 16 weeks of open label treatment with RISPERDAL CONSTA®, while continuing treatment as usual (mood stabilizers, antidepressants, and/or anxiolytics), were randomized to RISPERDAL CONSTA® or placebo, as adjunct to their treatment as usual, for up to 52 weeks. RISPERDAL CONSTA® is not indicated as adjunctive maintenance treatment in bipolar disorder.

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of patients experiencing adverse events, events were grouped into standardized categories using MedDRA terminology.

Monotherapy

Adverse Events Associated with Discontinuation of Treatment

In the 24-month, double-blind, placebo-controlled trial evaluating RISPERDAL CONSTA® as monotherapy maintenance treatment in patients with bipolar I disorder per study protocol, an adverse event was not recorded as the reason for discontinuation when a patient experienced a mood-related adverse event in association with relapse. One patient (0.6%) in the RISPERDAL CONSTA® group experienced an adverse event, hyperglycemia, that led to discontinuation and was not associated with relapse. Thirty-three patients (22%) in the placebo group and 15 patients (9.7%) in the RISPERDAL CONSTA® group who discontinued double-blind treatment due to relapse had adverse events with action taken of permanent stop. For the majority of patients in both treatment groups these adverse events were psychiatric. Depression was the only psychiatric adverse event associated with discontinuation of more relapsed patients in the RISPERDAL CONSTA® group than in the placebo group (5% RISPERDAL CONSTA® versus 2% placebo).

Commonly Observed Adverse Events in the Controlled Clinical Trial

Table 1.2 enumerates adverse events that occurred at an incidence of 2% or more, and were at least as frequent among bipolar patients treated with RISPERDAL CONSTA® as patients treated with placebo in the 24-month, double-blind treatment period of the trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder.

Table 1.2: Treatment-Emergent Adverse Events Reported by ≥ 2% of Patients with Bipolar I Disorder Treated with RISPERDAL CONSTA® and Equal or Greater than Placebo as Monotherapy in a 24-month, Double-Blind, Placebo-Controlled Clinical Trial

MedDRA Body System or Organ Class/ Dictionary-derived Term	Percentage of Patients Reporting Event	
	Placebo (N=149)	RISPERDAL CONSTA® (N=154)
Psychiatric disorders		
Insomnia	6	8
Depression	2	6
Nervous system disorders		
Headache	7	7
Dizziness	1	3
Infections and infestations		
Nasopharyngitis	3	4
Viral infection	1	2
General disorders and administration site conditions		
Fatigue	3	4
Asthenia	1	2
Gastrointestinal disorders		
Diarrhea	1	2
Nausea	1	2
Investigations		
Weight increased	1	5
Musculoskeletal and connective tissue disorders		
Back pain	3	3
Vascular disorders		
Hypertension	1	3

Serious Adverse Events

In the 24-month, placebo-controlled monotherapy trial, the most frequently reported serious adverse events in the RISPERDAL CONSTA® group during the double-blind period were psychiatric disorders: depression (3% RISPERDAL CONSTA® versus 1% placebo), Bipolar I disorder (2% RISPERDAL CONSTA® versus 6% placebo), and mania (2% RISPERDAL CONSTA® versus 7% placebo).

Less Common Clinical Trial Adverse Events (≤1%)

All reported events in the RISPERDAL CONSTA® group during the double-blind treatment period of the monotherapy trial reported at least as frequently in the placebo group are listed below except those already listed in Table 1.2.

Psychiatric disorders: Depressed mood, Libido decreased, Drug dependence.

Nervous system disorders: Akathisia, Dyskinesia, Parkinsonism, Hypoesthesia, Radiculitis, Sedation, Sinus headache, Somnolence, Tremor.

Infections and infestations: Bronchitis, Anogenital warts, Bacteriuria, Ear infection, Fungal infection, Furuncle, Gastroenteritis viral, Influenza, Onychomycosis, Papilloma viral infection, Paronychia, Pharyngitis streptococcal, Sinusitis, Tinea infection, Urinary tract infection, Viral upper respiratory tract infection.

General disorders and administration site conditions: Pyrexia, Feeling cold, Pain, Thirst.

Gastrointestinal disorders: Abdominal pain, Constipation, Dry mouth, Duodenal ulcer, Gastritis, Gingival bleeding, Hemorrhoids, Mouth ulceration, Salivary hypersecretion, Tooth loss, Vomiting.

Investigations: Electrocardiogram QT prolonged, Electrocardiogram T wave abnormal, Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased.

Metabolism and nutrition disorders: Decreased appetite, Dehydration, Hyperglycemia, Anorexia, Diabetes mellitus, Hypertriglyceridemia, Increased appetite, Obesity, Type 2 diabetes mellitus.

Musculoskeletal and connective tissue disorders: Musculoskeletal pain, Myalgia.

Reproductive system and breast disorders: Erectile dysfunction, Sexual dysfunction, Ejaculation disorder.

Cardiac disorders: Bundle branch block right, Myocardial ischemia.

Respiratory, thoracic and mediastinal disorders: Cough, Nasal congestion, Nasal polyps, Pharyngolaryngeal pain, Sinus congestion.

Blood and lymphatic disorders: Anemia, Lymphadenitis.

Eye disorders: Conjunctivitis, Visual disturbance.

Skin and subcutaneous tissue disorders: Dermatitis, Dermatitis contact.

Ear and labyrinth disorders: Ear pain.

Immune system disorders: Hypersensitivity.

Renal and urinary disorders: Stress urinary incontinence.

Adjunctive Therapy

Adverse Events Associated with Discontinuation of Treatment

In the 52-week, double-blind phase of the placebo-controlled trial in which RISPERDAL CONSTA® was administered as adjunctive therapy to patients with bipolar disorder in addition to their treatment as usual, approximately 4% (3/72) of patients treated with RISPERDAL CONSTA® discontinued due to an adverse event, compared with 1.5% (1/67) of placebo-treated patients. Adverse events that led to discontinuation that occurred more frequently in the RISPERDAL CONSTA® group were hypokinesia, tardive dyskinesia and hypertensive heart disease (1.4%, one patient each).

Commonly Observed Adverse Events in the Controlled Clinical Trial

Table 1.3 enumerates adverse events that occurred at an incidence of 2% or more, and were at least as frequent among bipolar patients treated with RISPERDAL CONSTA® as patients treated with placebo in the 52-week trial in which RISPERDAL CONSTA® was administered as adjunctive therapy to patients with bipolar disorder in addition to continuing with their treatment as usual. RISPERDAL CONSTA® is not indicated as adjunctive maintenance treatment in bipolar disorder.

Table 1.3: Treatment-Emergent Adverse Events Reported by ≥ 2% of Patients with Bipolar Disorder Treated with RISPERDAL CONSTA® and Equal or Greater than Placebo as Adjunctive Therapy in a 52-week, Double-Blind, Placebo-Controlled Clinical Trial

MedDRA Body System or Organ Class/ Dictionary-derived Term	Percentage of Patients Reporting Event	
	Placebo (N=67)	RISPERDAL CONSTA® (N=72)
Nervous system disorders		
Tremor	16	24
Parkinsonism[a]	6	15
Akathisia	6	6
Dyskinesia[b]	3	6
Sedation	0	6
Memory impairment	3	4
Disturbance in attention	0	4
Psychiatric disorders		
Irritability	3	3
Sleep disorder	3	3
Musculoskeletal and connective tissue disorders		
Arthralgia	3	4
Musculoskeletal stiffness	0	3
General disorders and administration site conditions		
Gait abnormal	0	4
Infections and infestations		
Upper respiratory tract infection	3	6
Nasopharyngitis	3	3
Urinary tract infection	2	3
Metabolism and nutrition disorders		
Decreased appetite	2	6
Increased appetite	0	4
Gastrointestinal disorders		
Loose stools	2	4
Salivary hypersecretion	3	3
Investigations		
Weight increased	2	7
Reproductive system and breast disorders		
Amenorrhea	2	4
Respiratory, thoracic and mediastinal disorders		
Cough	2	4
Dyspnea exertional	0	3
Skin and subcutaneous tissue disorders		
Alopecia	0	3
Eye disorders		
Visual acuity reduced	0	3
Vascular disorders		
Orthostatic hypotension	0	3

[a] Parkinsonism includes muscle rigidity, hypokinesia, cogwheel rigidity, and bradykinesia.
[b] Dyskinesia includes muscle twitching and dyskinesia.

Serious Adverse Events

In the 52-week, placebo-controlled adjunctive therapy trial, the most frequently reported serious adverse events in the RISPERDAL CONSTA® group during the double-blind period was mania (4% RISPERDAL CONSTA® versus 6% placebo).

Less Common Clinical Trial Adverse Events (≤ 1%)

All reported events in the RISPERDAL CONSTA® group during the double-blind treatment period of the adjunctive therapy trial reported at least as frequently in the placebo group are listed below except those already listed in Table 1.3.

Nervous system disorders: Cogwheel rigidity, Drooling, Neuritis, Tardive dyskinesia.

Psychiatric disorders: Anxiety, Libido decreased, Middle insomnia, Panic attack, Suicide attempt.

Musculoskeletal and connective tissue disorders: Pain in extremity, Posture abnormal.

General disorders and administration site conditions: Chest pain, Malaise, Pain.

Infections and infestations: Fungal infection, Furuncle, Pneumonia, Sinusitis, Tuberculosis

Metabolism and nutrition disorders: Anorexia, Hyperlipidemia.

Gastrointestinal disorders: Hemorrhoidal hemorrhage, Hemorrhoids, Halitosis, Tongue Disorder.

Investigations: Corneal reflex decreased, urine analysis abnormal.

Reproductive system and breast disorders: Menorrhagia, Menstrual disorder

Respiratory, thoracic and mediastinal disorders: Dyspnea.

Skin and subcutaneous tissue disorders: Alopecia areata, Dry skin, Face edema, Pain of skin, Seborrhoeic dermatitis.

Eye disorders: Cataract.

Vascular disorders: Hypotension.

Blood and lymphatic disorders: Anemia.

Cardiac disorders: Hypertensive heart disease.

Endocrine disorders: Hypothyroidism.

Injury, poisoning and procedural complications: Blister.

Renal and urinary disorders: Enuresis.

Adverse Events Observed Across Indications

Extrapyramidal Symptoms

Schizophrenia

Two methods were used to measure extrapyramidal symptoms (EPS) in the 12-week, placebo-controlled trial comparing three doses of RISPERDAL CONSTA® (25 mg, 50 mg, and 75 mg) with placebo including: 1) the incidence of spontaneous reports of EPS symptoms; and 2) the change from baseline to endpoint on the total score (sum of the subscale scores for parkinsonism, dystonia, and dyskinesia) of the Extrapyramidal Symptom Rating Scale (ESRS).

As shown in Table 1.1, the overall incidence of EPS-related adverse events (akathisia, dystonia, parkinsonism, and tremor) in patients treated with 25 mg RISPERDAL CONSTA® was comparable to that of patients treated with placebo; the incidence of EPS-related adverse events was higher in patients treated with 50 mg RISPERDAL CONSTA®.

The median change from baseline to endpoint in total ESRS score showed no worsening in patients treated with RISPERDAL CONSTA® compared with patients treated with placebo: 0 (placebo group); -1 (25 mg group, significantly less than the placebo group); and 0 (50 mg group).

Bipolar Disorder

There were no clinically meaningful changes from baseline to study endpoint for mean ESRS total score during any phase of the monotherapy study. Similarly, there were no meaningful changes from baseline to study endpoint on dyskinetic symptoms (measured using the Abnormal Involuntary Movement Scale), akathisia symptoms (Barnes Akathisia Scale) or Parkinsonian symptoms (Simpson-Angus Rating Scale) during any phase of the adjunctive therapy study. As shown in Table 1.3, a higher incidence of EPS-related adverse events was noted in the adjunctive therapy study, predominantly tremor.

Vital Sign Changes

Hypotension (including orthostatic) and tachycardia have been observed following the administration of RISPERDAL CONSTA®. In the placebo-controlled trial in patients with schizophrenia, orthostatic hypotension was observed in 2% of patients treated with 25 mg or 50 mg RISPERDAL CONSTA® (see **WARNINGS AND PRECAUTIONS — Cardiovascular**).

Weight Changes

In the 12-week, placebo-controlled trial, 9% of patients with schizophrenia treated with RISPERDAL CONSTA® (25 or 50 mg), compared with 6% of patients treated with placebo, experienced a weight gain of >7% of body weight at endpoint.

In the 24-month, double-blind, placebo-controlled treatment period of the trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as monotherapy for

maintenance treatment in patients with bipolar I disorder, 11.6% of patients treated with RISPERDAL CONSTA® compared with 2.8% of patients treated with placebo experienced a weight gain of >7% of body weight at endpoint (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**).

ECG Changes

Compared with placebo, there were no statistically significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL CONSTA® in the 12-week, placebo-controlled trial in patients with schizophrenia (see **WARNINGS AND PRECAUTIONS — General,** QT Interval).

The electrocardiograms of 227 patients were evaluated in the 24-month double-blind, placebo-controlled treatment period of a trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder. There were no clinically relevant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL CONSTA® compared to placebo (see **WARNINGS AND PRECAUTIONS — General,** QT Interval).

Pain Assessment and Local Injection Site Reactions

Gluteal

The mean intensity of injection pain reported by patients with schizophrenia using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 16.7 to 12.6; 25 mg: 12.0 to 9.0; 50 mg: 18.2 to 11.8). After the sixth injection (Week 10), investigator ratings indicated that 1% of patients treated with 25 mg or 50 mg RISPERDAL CONSTA® experienced redness, swelling, or induration at the injection site.

Deltoid

In a separate study to observe local-site tolerability, RISPERDAL CONSTA® was administered into the deltoid muscle every 2 weeks over a period of 8 weeks, (patients received up to 2 injections per arm as alternate arms were injected). No patient discontinued treatment due to local injection site pain or reaction. Clinician ratings indicated that only mild redness, swelling, or induration at the injection site was observed in subjects treated with 37.5 mg or 50 mg RISPERDAL CONSTA® at 2 hours after deltoid injection. All ratings returned to baseline at the predose assessment of the next injection 2 weeks later. No moderate or severe reactions were observed in any subject.

The tolerability of repeated injections of RISPERDAL CONSTA® in the deltoid muscle for more than 8 weeks has not been systematically studied.

Hyperprolactinemia

RISPERDAL CONSTA® elevated plasma prolactin levels. Possible manifestations associated with elevated prolactin levels are nonpuerperal lactation, amenorrhea, abnormal sexual function, ejaculation failure, decreased libido, and impotence.

Other Adverse Events
As with other antipsychotics, cases of water intoxication, either due to polydipsia or to syndrome of inappropriate secretion of antidiuretic hormone (SIADH), have occasionally been reported during treatment with RISPERDAL®.

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory Changes
The percentage of patients treated with RISPERDAL CONSTA® who experienced potentially important changes in routine serum chemistry, hematology, or urinalysis parameters was similar to or less than that of placebo patients. Additionally, no patients discontinued treatment due to changes in serum chemistry, hematology, or urinalysis parameters.

In one study with oral RISPERDAL® in which testosterone levels were measured, testosterone decreased below the normal range in 6 out of 85 patients.

Adverse Reactions Reported with Paliperidone and Oral Risperidone
Paliperidone is the active metabolite of risperidone. Therefore, the adverse reaction profiles of both the oral and injectable formulations of paliperidone are relevant to one another and, also, to risperidone. In addition to the above adverse reactions, the following adverse reactions, classified using MedDRA terminology, have been noted with the use of paliperidone and /or risperidone products and can be expected to occur with both the oral and injectable formulations of risperidone.

Blood and Lymphatic System Disorders: Eosinophil count increased, Hematocrit decreased, Neutropenia, White blood cell count decreased

Cardiac Disorders: Atrioventricular block, Postural orthostatic tachycardia syndrome, Sinus arrhythmia

Ear and Labyrinth Disorders: Tinnitus

Endocrine Disorders: Glucose urine present

Eye Disorders: Dry eye, Eye movement disorder, Eye rolling, Eyelid margin crusting, Glaucoma, Lacrimation increased, Ocular hyperemia

Gastrointestinal Disorders: Cheilitis, Dysphagia, Fecal incontinence, Fecaloma, Flatulence, Gastroenteritis, Intestinal obstruction, Swollen tongue

General Disorders and Administration Site Conditions: Body temperature decreased, Body temperature increased, Chills, Discomfort, Drug withdrawal syndrome, Face edema, Induration, Malaise, Peripheral coldness, Thirst

Hepatobiliary disorders: Transaminases increased

Infections and Infestations: Acarodermatitis, Bronchitis, Cellulitis, Cystitis, Eye infection, Localised infection, Respiratory tract infection, Subcutaneous abscess, Tonsillitis, Viral infection

Injury, Poisoning and Procedural Complications: Fall, Procedural pain

Immune System Disorders: Anaphylactic reaction

Metabolism and Nutrition Disorders: Blood cholesterol increased, Blood triglycerides increased, Hyperinsulinaemia, Polydipsia

Musculoskeletal, Connective Tissue, and Bone Disorders: Blood creatine phosphokinase increased, Joint swelling, Neck pain, Posture abnormal, Rhabdomyolysis

Nervous System Disorders: Balance disorder, Cerebrovascular accident, Cerebrovascular disorder, Convulsion (includes Grand mal convulsion), Coordination abnormal, Depressed level of consciousness, Diabetic coma, Dystonia (includes blepharospasm, cervical spasm, emprosthotonus, facial spasm, hypertonia, laryngospasm, muscle contractions involuntary, myotonia, oculogyration, opisthotonus, oropharyngeal spasm, pleurothotonus, risus sardonicus, tetany, tongue paralysis, tongue spasm, torticollis, trismus) , Head titubation, Loss of consciousness, Neuroleptic malignant syndrome, Psychomotor hyperactivity, Unresponsive to stimuli

Psychiatric Disorders: Anorgasmia, Blunted affect

Renal and Urinary Disorders: Dysuria, Pollakiuria

Reproductive System and Breast Disorders: Breast discharge, Breast engorgement, Breast enlargement, Gynecomastia, Menstrual disorder (includes Menstruation irregular, Oligomenorrhea), Menstruation delayed, Sexual dysfunction, Vaginal discharge

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

Skin and Subcutaneous Disorders: Drug eruption, Eczema, Erythema, Hyperkeratosis, Skin discolouration, Skin lesion, Urticaria

Post-Market Adverse Drug Reactions

Adverse events first identified during post-marketing experience with risperidone are included in Table 1.4. In Table 1.4, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 1.4 Adverse Drug Reactions Identified During Postmarketing Experience with Risperidone by Frequency Category Estimated from Spontaneous Reporting Rates

Blood and Lymphatic Disorders	
Very rare	Thrombocytopenia
Endocrine Disorders	
Very rare	Inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders	
Very rare	Diabetes mellitus, Diabetic ketoacidosis, Hypoglycemia, Water intoxication
Psychiatric Disorders	
Very rare	Mania
Nervous System Disorders	
Very rare	Dysgeusia
Immune System Disorders	
Rare	Hypersensitivity *(including very rare events of angioedema, anaphylaxis, and anaphylactic shock)*
Eye Disorders	
Very rare	Floppy iris syndrome (intraoperative)
Cardiac Disorders	
Very rare	Atrial fibrillation
Vascular Disorders	
Very rare	Deep vein thrombosis
Respiratory, Thoracic, and Mediastinal Disorders	
Very rare	Sleep apnea syndrome
Gastrointestinal Disorders	
Very rare	Pancreatitis, Ileus
Skin and Subcutaneous Tissue Disorders	
Very rare	Alopecia, Angioedema
Reproductive System and Breast Disorders	
Very rare	Priapism
General Disorders	
Very rare	Hypothermia

In addition, adverse events reported with risperidone treatment since market introduction which were temporally related to risperidone therapy include the following: agitation, skin manifestations of allergy including cases of Stevens-Johnson syndrome, systemic manifestations of allergy including a case of anaphylactic shock, apnea, benign pituitary adenomas, and Parkinson's disease aggravated. Cerebrovascular adverse events, including cerebrovascular accidents and transient ischemic attacks, have been reported during treatment with RISPERDAL® (see **WARNINGS AND PRECAUTIONS — Special Populations, Use in Geriatric Patients with Dementia**, Cerebrovascular Adverse Events (CVAEs) in Elderly Patients with Dementia). Hyperglycemia and exacerbation of pre-existing diabetes have been

reported during treatment with risperidone (see **WARNINGS AND PRECAUTIONS — Endocrine and Metabolism**).

As with other neuroleptics, sudden deaths have been reported during treatment with risperidone. Most of the patients had pre-existing cardiovascular disease or were morbidly obese. A relationship to risperidone has not been established at this time.

Retinal artery occlusion after injection of RISPERDAL CONSTA® has been reported very rarely during post-marketing surveillance. RISPERDAL CONSTA® should be injected into the gluteal or deltoid muscle, and care must be taken to avoid inadvertent injection of RISPERDAL CONSTA® into a blood vessel (see **DOSAGE AND ADMINISTRATION**).

Injection site reactions including injection site abscess, cellulitis, cyst, hematoma, necrosis, nodule, and ulcer have been reported with RISPERDAL CONSTA®. These events were reported as serious. Isolated cases required surgical intervention.

As with other neuroleptics, sudden death, torsades de pointes, ventricular tachycardia, arrhythmia, cardiopulmonary arrest and QT prolongation have been reported during treatment with risperidone. Many of the patients had pre-existing cardiovascular disease, were on concomitant medications known to prolong the QT interval, had risk factors for QT prolongation, took an overdose of risperidone, and/or were morbidly obese. Very rarely, QT prolongation has been reported in the absence of confounding factors.

Significant weight gain has been reported in both clinical trials and post-marketing (see **WARNINGS AND PRECAUTIONS — Endocrine and Metabolism**).

In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including RISPERDAL®. Granuloycytopenia and agranulocytosis have also been reported (see **WARNINGS AND PRECAUTIONS - Hematologic**).

In post-marketing experience, drug withdrawal syndrome neonatal has been reported very rarely.

Atypical antipsychotic drugs, such as risperidone, have been associated with cases of sleep apnea, with or without concomitant weight gain. In patients who have a history of, or that are at risk of, sleep apnea, RISPERDAL CONSTA® should be prescribed with caution.

Risks of somnambulism (sleep walking) and sleep-related eating disorder have been associated with the use of atypical antipsychotics including RISPERDAL CONSTA®.

Hypersensitivity

There have been very rare spontaneous reports of severe hypersensitivity (e.g., anaphylaxis, angioedema, anaphylactic shock) in some patients after injection with RISPERDAL CONSTA®. Symptoms of anaphylaxis include skin rash, hives, peripheral edema, swollen eye, tongue and face, hyperhidrosis, dyspnea, and hypotension. It is unknown as to how many of these patients previously tolerated oral risperidone or paliperidone. However, anaphylactic-type reactions have occurred after

injection with RISPERDAL CONSTA® in patients who have previously tolerated oral risperidone or oral paliperidone (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS**, **Immune**, Hypersensitivity and **DOSAGE AND ADMINISTRATION).**

DRUG INTERACTIONS

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

Overview

Centrally-acting Drugs and Alcohol

Given the primary central nervous system effects of RISPERDAL CONSTA®, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

Levodopa and Dopamine Agonists

RISPERDAL CONSTA® may antagonize the effects of levodopa and dopamine agonists.

Drugs with Hypotensive Effects

Because of its potential for inducing hypotension, RISPERDAL CONSTA® may enhance the hypotensive effects of other therapeutic agents.

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

Drugs Known to Prolong the QT interval

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

Drug-Drug Interactions

Risperidone is mainly metabolized 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 (risperidone and 9-hydroxyrisperidone combined). 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

Co-administration of RISPERDAL CONSTA® with a strong CYP3A4 and/or P-gp inhibitor may

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

CYP3A4 and/or P-gp Inducers

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

Highly Protein-bound Drugs

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

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

Concomitant Use with Furosemide

See **WARNINGS AND PRECAUTIONS** regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide and oral RISPERDAL®.

The Effect of Other Drugs on the Metabolism of Risperidone

SSRIs and Tricyclic Antidepressants

Fluoxetine: Fluoxetine , a strong CYP 2D6 inhibitor, increases the plasma concentration of risperidone but less so of risperidone and 9-hydroxyrisperidone combined. Pharmacokinetic interaction with fluoxetine was examined in a study which measured steady-state plasma levels of oral risperidone and its metabolites before and following 3 weeks of co-treatment with fluoxetine (n=10). The addition of fluoxetine resulted in about a 2- to 3-fold increase in peak and AUC levels of risperidone and about a 50% increase in peak and AUC levels for risperidone and 9-hydroxyrisperidone combined.

Paroxetine: Paroxetine, a strong CYP 2D6 inhibitor, increases the plasma concentration of risperidone but, at dosages up to 20 mg/day, less so of risperidone and 9-hydroxyrisperidone combined. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction. Pharmacokinetic interaction with paroxetine was examined in a study which measured steady-state plasma levels of risperidone and its metabolites before and following 4 weeks of co-treatment with paroxetine (n=10). After 4 weeks of paroxetine treatment, the sum of the concentrations of risperidone and 9-hydroxyrisperidone increased significantly by 45% over baseline.

When fluoxetine or paroxetine is initiated in patients receiving the recommended dose of 25 mg of RISPERDAL CONSTA®, it is recommended to continue treatment with the 25 mg dose unless clinical judgment necessitates lowering the RISPERDAL CONSTA® dose to 12.5 mg or necessitates interruption of treatment with RISPERDAL CONSTA®. When RISPERDAL CONSTA® is initiated in patients already receiving fluoxetine or paroxetine, a starting dose of 12.5 mg can be considered. The efficacy of the 12.5 mg dose has not been investigated in clinical trials (see also **DOSAGE AND ADMINISTRATION**).

Tricyclic antidepressants: Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction.

Sertraline: Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.

Antibacterials

Erythromycin: Erythromycin, a moderate CYP 3A4 inhibitor, did not change the pharmacokinetics of risperidone or risperidone and 9-hydroxyrisperidone combined. Risperidone was administered as a single dose of 1 mg with multiple doses of erythromycin (500 mg q.i.d.) in healthy volunteers (n=18).

Rifampicin: Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.

Anticholinesterases

Galantamine and Donepezil: Galantamine (n=15) and donepezil (n=24), both CYP2D6 and CYP3A4 substrates, did not show an effect on the pharmacokinetics of risperidone or risperidone and 9-hydroxyrisperidone combined. Galantamine 12 mg o.d. was co-administered with risperidone 0.5 mg o.d. in healthy elderly volunteers. Donepezil 5 mg o.d. was co-administered with risperidone 0.5 mg b.i.d. in healthy male volunteers.

Antiepileptics

Carbamazepine and Other CYP 3A4 Enzyme Inducers

Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease substantially the plasma levels of risperidone and its active metabolite 9-hydroxyrisperidone (n=11). Similar effects may be observed with other CYP 3A4 hepatic enzyme inducers. Consequently, in the presence of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dose of RISPERDAL CONSTA® may have to be adjusted. At the initiation of therapy with carbamazepine or other known CYP 3A4 hepatic enzyme inducers, patients should be closely monitored for the first 4–8 weeks, since the dose of RISPERDAL CONSTA® may need to be adjusted. A dose increase, or additional oral RISPERDAL®, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 hepatic inducers, the dosage of RISPERDAL CONSTA® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL CONSTA® between 2 and 4 weeks before the planned discontinuation of carbamazepine or other CYP 3A4 inducers to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the recommended dose (25 mg) of RISPERDAL CONSTA®, it is recommended to continue treatment with the 25 mg dose unless clinical judgment necessitates lowering the RISPERDAL CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL CONSTA® treatment (see also **DOSAGE AND ADMINISTRATION**). The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Topiramate:
Healthy Volunteers: A drug-drug interaction study between risperidone and topiramate was conducted in 12 healthy volunteers (6 males, 6 females), ages 28–40 years, with single-dose administration of risperidone (2 mg) and multiple doses of topiramate (titrated up to 200 mg/day). In the presence of topiramate, systemic exposure of risperidone and 9-hydroxyrisperidone combined was reduced such that mean AUC_{0-4} was 11% lower and mean C_{max} was statistically significantly (18%) lower. In the presence of topiramate, systemic exposure of risperidone was statistically significantly reduced such that mean C_{max} and AUC_{0-4} were 29% and 23% lower, respectively. The pharmacokinetics of 9-hydroxyrisperidone were unaffected. The effects of a single dose (2 mg/day) of risperidone on the pharmacokinetics of multiple doses of topiramate have not been studied.

Patients with Bipolar Disorder: A drug-drug interaction study conducted in 52 patients with various types of bipolar disorder (24 males, 28 females), ages 19–56 years, evaluated the steady-state pharmacokinetics of risperidone and topiramate when administered concomitantly. Eligible subjects were stabilized on a risperidone dose of 1–6 mg/day for 2 to 3 weeks. Topiramate was then titrated up to escalating doses of 100, 250 and 400 mg/day along with risperidone for up to 6 weeks. Risperidone was then tapered and discontinued over 4 weeks while maintaining topiramate (up to 400 mg/day). There was a statistically significant reduction in risperidone systemic exposure (16% and 33% for AUC_{12} and 13% and 34% for C_{max} at the 250 and 400 mg/day doses, respectively). Minimal alterations were observed in the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined and 9-hydroxyrisperidone. Topiramate systemic exposure was slightly reduced (12.5% for mean C_{max} and 11% for mean AUC_{12}) in the presence of risperidone, which achieved statistical significance. There were no clinically significant changes in the systemic exposure of risperidone and 9-hydroxyrisperidone combined or of topiramate. The effects of higher doses of topiramate (> 400 mg/day) are unknown. Therefore, if combination therapy is chosen, patients receiving both risperidone and topiramate should be closely monitored.

Antifungals
Itraconazole: 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: 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: Phenothiazines may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Clozapine: Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Antivirals

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

Beta-Blockers

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

Calcium Channel Blockers

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

Gastrointestinal Drugs

Cimetidine and Ranitidine (H_2-receptor antagonists): Risperidone was administered as a single dose of 1 mg with multiple doses of either cimetidine (400 mg b.i.d.) or ranitidine (150 mg b.i.d.), both weak inhibitors of CYP2D6 and CYP3A4, in healthy young volunteers (n=12). The effect of the drug interaction of cimetidine and ranitidine on risperidone and 9-hydroxyrisperidone combined was minimal.

Effects of Risperidone on the Metabolism of Other Drugs

Aripiprazole: A CYP2D6 and CYP3A4 substrate; Risperidone tablets or injections did not affect the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.

Lithium: Oral risperidone (3 mg b.i.d.) did not show an effect on the pharmacokinetics of lithium (400, 450, or 560 b.i.d.) (n=13).

Valproate: Oral risperidone (4 mg o.d.) did not show an effect on the pharmacokinetics of valproate (1000 mg/day) (n=9). However, more subjects reported adverse events with the risperidone-valproate therapy compared to the placebo-valproate group in the clinical trial.

Digoxin: The effect of oral risperidone (0.5 mg/day administered b.i.d.) on the steady-state plasma concentrations of digoxin (0.125 mg/day) was examined in a double-blind, two-way crossover trial in 19 healthy elderly volunteers (median age 68 years, range 61 to 75 years). Risperidone did not affect the steady-state pharmacokinetics of digoxin, and concurrent administration of the two drugs was well tolerated.

In vitro studies, in which risperidone was given in the presence of various highly protein-bound agents, indicated that clinically relevant changes in protein binding would not occur either for RISPERDAL CONSTA® or for any of the drugs tested.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Centrally-acting Drugs and Alcohol
Given the primary central nervous system effects of RISPERDAL®, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

DOSAGE AND ADMINISTRATION

Dosing Considerations
RISPERDAL CONSTA® is a treatment option for patients where the risk of relapse requires intervention according to clinical judgment. For patients who have never taken oral RISPERDAL®/RISPERDAL M-TAB®, tolerability with oral RISPERDAL®/RISPERDAL M-TAB® should be established prior to initiating treatment with RISPERDAL CONSTA®.

Very rare cases of severe hypersensitivity after injection with RISPERDAL CONSTA® have been reported during post-marketing experience in patients who have previously tolerated oral risperidone or oral paliperidone. Care should be taken to avoid exposure to those that are suspected to be hypersensitive or have shown hypersensitivity reactions to any of the excipients (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

- Patients prone to hypotension
- Geriatrics
- Patients with renal impairment
- Patients with hepatic impairment

Administration
RISPERDAL CONSTA® should be administered every 2 weeks by deep intramuscular gluteal or deltoid injection. Each injection should be administered by a healthcare professional using the appropriate enclosed safety needle (see **Instructions for Use**). When selecting an intramuscular site for injection, it is recommended that the healthcare professional conduct an assessment of the patient and site characteristics considering such factors as age, physical condition, skin integrity and size of the muscle.

For gluteal administration, use the 2-inch needle alternating injections between the two buttocks. For deltoid administration, use the 1-inch needle alternating injections between the two arms. Prior to each administration, the site of injection should be examined for any signs of clinically significant or persistent local reaction. If such signs are present, an alternate site should be chosen for injection. Care must be taken to avoid inadvertent injection of RISPERDAL CONSTA® into a blood vessel. Do **not** administer intravenously (see **WARNINGS AND PRECAUTIONS — General** and **Instructions for Use**).

While gluteal and deltoid injections of RISPERDAL CONSTA® have demonstrated bioequivalence under the recommended injection parameters, the tolerability of repeated injections of RISPERDAL CONSTA® in the deltoid muscle for more than 8 weeks has not been systematically studied.

Recommended Dose and Dosage Adjustment

Schizophrenia

The recommended dose is 25 mg IM every 2 weeks. Although dose response for effectiveness has not been established for RISPERDAL CONSTA®, some patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg RISPERDAL CONSTA® every 2 weeks. No additional benefit was observed with dosages greater than 50 mg RISPERDAL CONSTA® in clinical trials in patients with schizophrenia; however, a higher incidence of adverse effects was observed.

Although no controlled studies have been conducted to answer the question of how long patients should be treated with RISPERDAL CONSTA®, oral RISPERDAL®/RISPERDAL M-TAB® has been shown to be effective in maintaining clinical improvement during long-term therapy (1 year) in patients with schizophrenia. It is recommended that responding patients be continued on treatment with RISPERDAL CONSTA® at the lowest dose needed. Patients should be periodically reassessed to determine the need for continued treatment.

Bipolar Disorder

The recommended dose is 25 mg IM every 2 weeks. Although dose response for effectiveness has not been established for RISPERDAL CONSTA®, some patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. In clinical trials the majority of patients were treated with the 25 mg dose. The maximum dose should not exceed 50 mg RISPERDAL CONSTA® every 2 weeks. Doses above 50 mg have not been studied in this population. It is recommended that responding patients be continued with the lowest dose needed and reassessed periodically to determine the need for continued treatment.

RISPERDAL CONSTA® is not indicated as adjunctive treatment in patients with bipolar disorder.

General Dosing Information

A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with hepatic or renal impairment (see below), for certain drug interactions that increase risperidone plasma concentrations (see **DRUG INTERACTIONS**), or in patients who have a history of poor tolerability to psychotropic medications. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Oral RISPERDAL®/RISPERDAL M-TAB® (or another antipsychotic medication) should be given with the first injection of RISPERDAL CONSTA® and continued for 3 weeks to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (see **ACTION AND CLINICAL PHARMACOLOGY**).

Upward dose adjustment should not be made more frequently than every 4 weeks. The clinical effects of this dose adjustment should not be anticipated earlier than 3 weeks after the first injection with the higher dose.

In patients with clinical factors such as hepatic or renal impairment, or for certain drug interactions that increase risperidone plasma concentrations (see **DRUG INTERACTIONS**), dose reduction as low as 12.5 mg may be appropriate. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Two different dose strengths of RISPERDAL CONSTA® should not be combined in a single administration.

Pediatric Use
RISPERDAL CONSTA® has not been studied in children younger than 18 years old.

Geriatrics
For elderly patients treated with RISPERDAL CONSTA®, the recommended dosage is 25 mg IM every 2 weeks. Oral RISPERDAL®/RISPERDAL M-TAB® (or another antipsychotic medication) should be given with the first injection of RISPERDAL CONSTA® and should be continued for 3 weeks to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (see **ACTION AND CLINICAL PHARMACOLOGY**). RISPERDAL CONSTA® has not been studied in elderly patients with bipolar disorder. Elderly patients and patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). These patients should avoid sodium depletion or dehydration, and circumstances that accentuate hypotension (alcohol intake, high ambient temperature, etc.). Monitoring of orthostatic vital signs should be considered (see **WARNINGS AND PRECAUTIONS — Cardiovascular**).

Patients with Hepatic Impairment
RISPERDAL CONSTA® has not been studied in hepatically impaired patients.

RISPERDAL CONSTA® should be used with caution in patients with hepatic impairment.

Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone and this may result in an enhanced effect. If hepatically impaired patients require treatment with RISPERDAL CONSTA®, a starting dose of 0.5 mg b.i.d. oral risperidone (e.g., RISPERDAL M-TAB®) is recommended during the first week. In the second week, 1 mg b.i.d. or 2 mg q.d. can be given. If an oral dose of at least 2 mg is well tolerated, an injection of 25 mg RISPERDAL CONSTA® can be administered every 2 weeks. Alternatively, a starting dose of 12.5 mg RISPERDAL CONSTA® may be appropriate (see **WARNINGS AND PRECAUTIONS — Hepatic/Biliary/Pancreatic** and **ACTION AND CLINICAL PHARMACOLOGY — Special Populations and Conditions**). The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower titration may be medically appropriate.

Patients with Renal Impairment
RISPERDAL CONSTA® has not been studied in renally impaired patients.

RISPERDAL CONSTA® should be used with caution in patients with renal impairment.

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults. If renally impaired patients require treatment with RISPERDAL CONSTA®, a starting dose of 0.5 mg b.i.d. oral risperidone (e.g., RISPERDAL M-TAB®) is recommended during the first week. In the second week, 1 mg b.i.d. or 2 mg q.d. can be given. If an oral dose of at least 2 mg is well tolerated, an injection of 25 mg RISPERDAL CONSTA® can be administered every 2 weeks. Alternatively, a starting dose of 12.5 mg RISPERDAL CONSTA® may be appropriate (see **WARNINGS AND PRECAUTIONS - Renal** and **ACTION AND CLINICAL PHARMACOLOGY — Special Populations and Conditions**). The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower titration may be medically appropriate.

Switching from Other Antipsychotics
There are no systematically collected data to specifically address switching patients from other antipsychotics to RISPERDAL CONSTA®, or concerning concomitant administration with other antipsychotics. Previous antipsychotics should be gradually discontinued to ensure that therapeutic concentrations are maintained during the 3 weeks after the first injection of RISPERDAL CONSTA® until the main release phase of risperidone from the injection site has begun. For patients who have never taken oral RISPERDAL®/RISPERDAL M-TAB®, it is recommended to establish tolerability with oral RISPERDAL®/RISPERDAL M-TAB® prior to initiating treatment with RISPERDAL CONSTA®. As recommended with other antipsychotic medications, the need for continuing existing EPS medication should be re-evaluated periodically.

Reinitiation of Treatment in Patients Previously Discontinued
There are no data to specifically address reinitiation of treatment. When restarting patients who have had an interval off treatment with RISPERDAL CONSTA®, supplementation with oral RISPERDAL® (or another antipsychotic medication) should be administered.

Instructions for Use
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®. RISPERDAL CONSTA® must be reconstituted only in the diluent supplied in the dose pack.

Do not substitute ANY components of the dose pack.

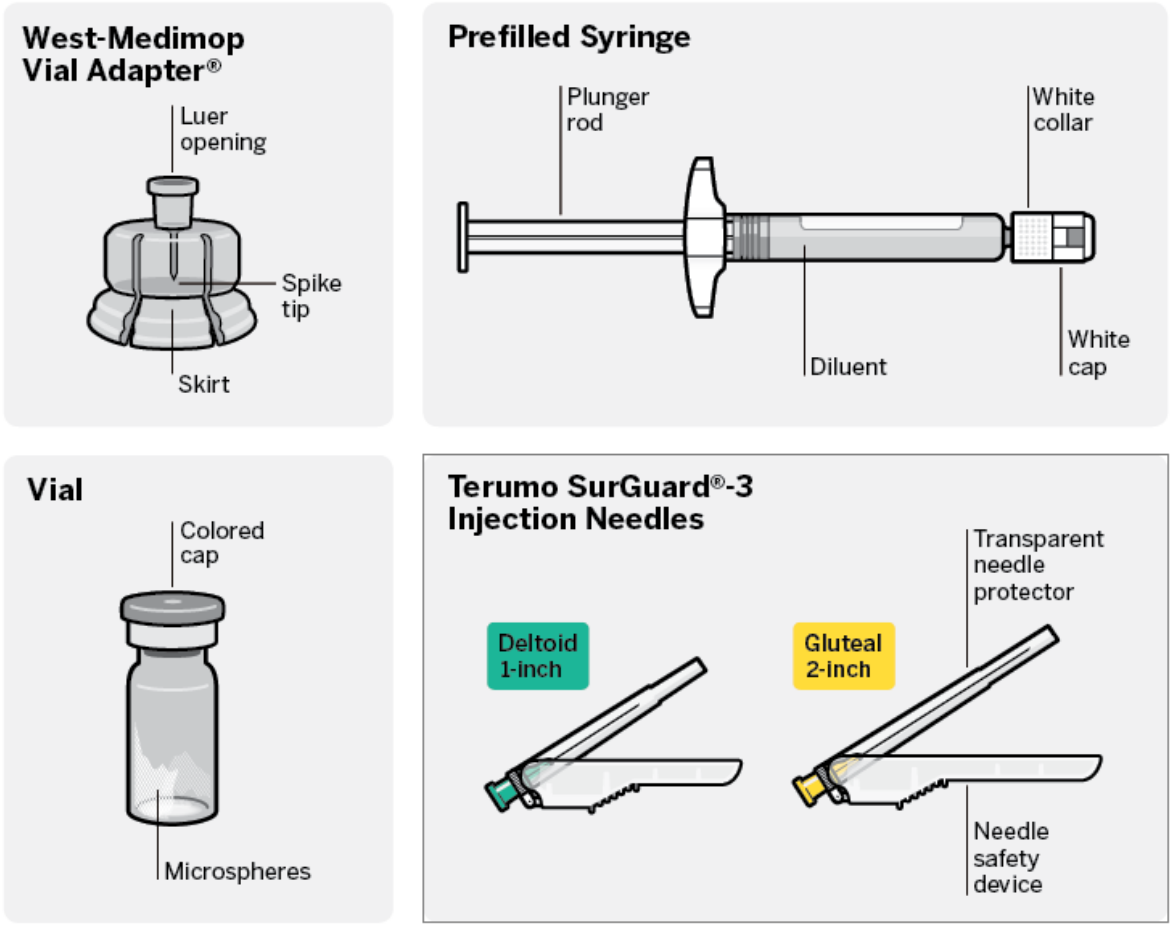
Do not store suspension after reconstitution
Administer dose as soon as possible after reconstitution to avoid settling.

Proper dosing
The entire contents of the vial must be administered to ensure intended dose of RISPERDAL CONSTA® is delivered.

SINGLE-USE DEVICE

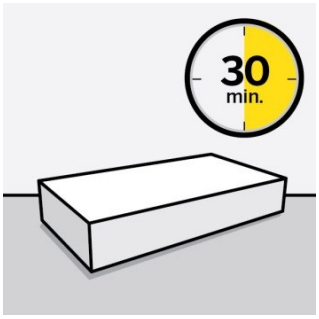
Do not reuse. Medical devices require specific material characteristics to perform as intended. These characteristics have been verified for single use only. Any attempt to re-process the device for subsequent re-use may adversely affect the integrity of the device or lead to deterioration in performance.

Dose pack contents



Step 1	Assemble components

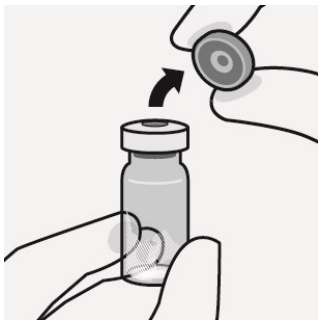
Take out dose pack



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.

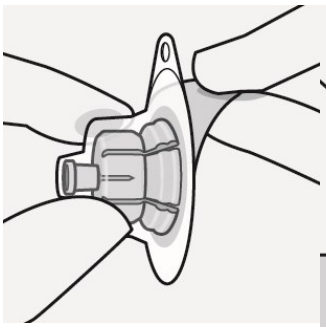
Connect vial adapter to vial



Remove cap from vial
Flip off colored cap from vial.

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

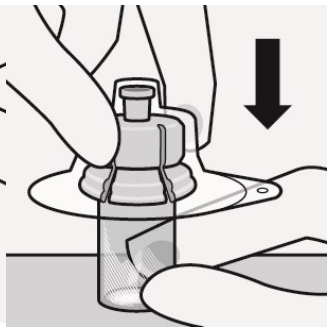
Do not remove grey rubber stopper.



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

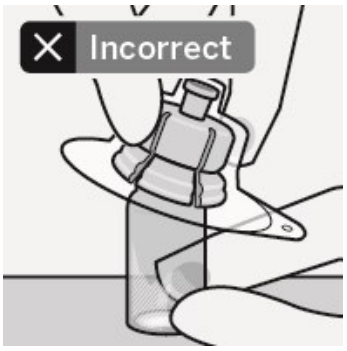
Do not remove vial adapter from blister.

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

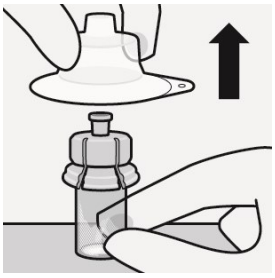


Connect vial adapter to vial
Place vial on a hard surface and hold by the base. Center vial adapter over the grey rubber stopper. Push vial adapter straight down onto vial top until it snaps securely into place.

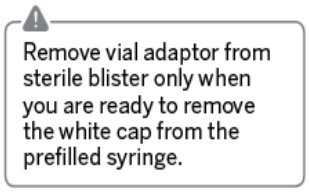
Do not place vial adapter on at an angle or diluent may leak upon transfer to the vial.



Connect prefilled syringe to vial adapter



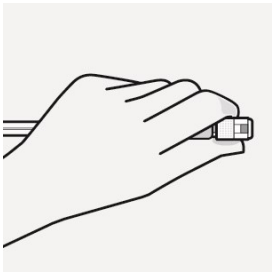
Remove sterile blister



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

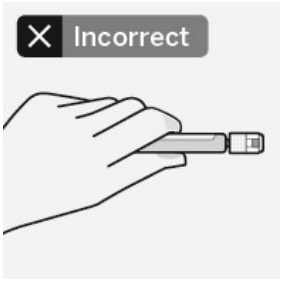
Do not shake.

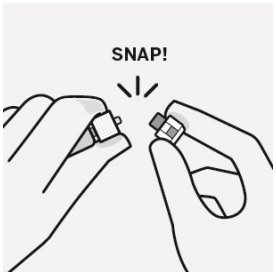
Do not touch exposed luer opening on vial adapter.
This will result in contamination.



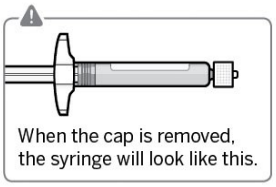
Use proper grip
Hold by white collar at the tip of the syringe.

Do not hold syringe by the glass barrel during assembly.

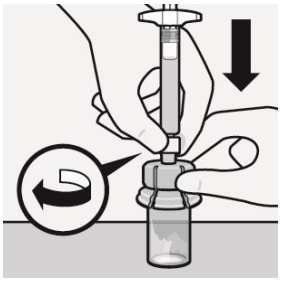




Remove cap
Holding the white collar, snap off the white cap.
Do not twist or cut off the white cap.
Do not touch syringe tip. This will result in contamination.

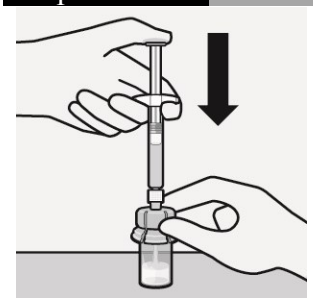


The broken-off cap can be discarded.



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.

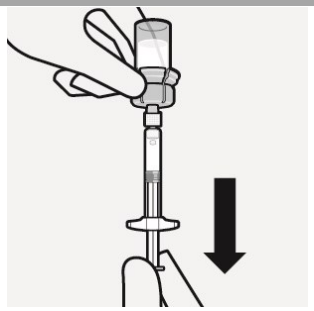
Step 2	Reconstitute microspheres



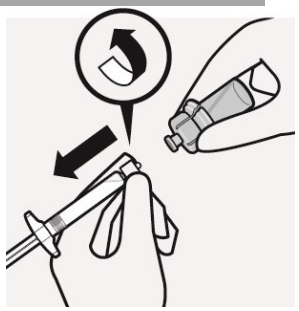
Inject diluent
Inject entire amount of diluent from syringe into the vial.

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 <u>vigorously</u> for at least 10 seconds**, as shown.
<u>Check the suspension</u>. 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.

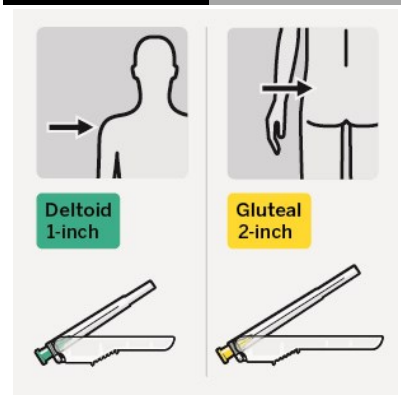


Transfer suspension to syringe
Invert vial completely. Slowly pull plunger rod down to withdraw entire contents from the vial into the syringe.

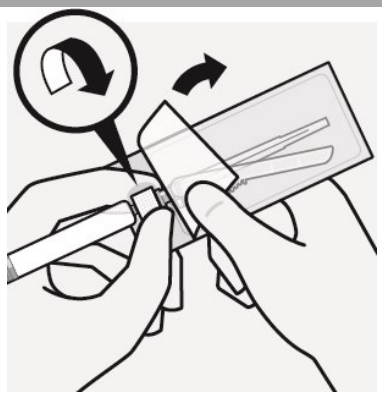


Remove vial adapter
Hold white collar on the syringe and unscrew from vial adapter.
Tear section of the vial label at the perforation. Apply detached label to the syringe for identification purposes.
Discard both vial and vial adapter appropriately.

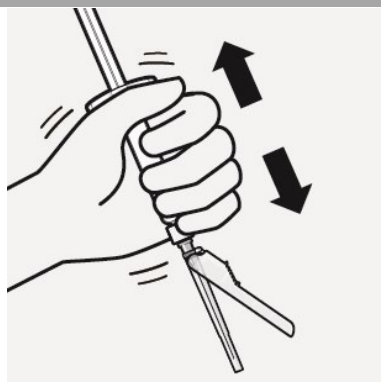
Step 3	Attach needle



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

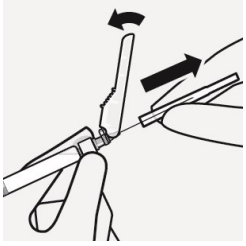


Attach needle
Peel blister pouch open part way and use to grasp the base of the needle, as shown.
Holding the white collar on the syringe, attach syringe to needle luer connection with a firm **clockwise twisting motion** until snug.
Do not touch needle luer opening. This will result in contamination.

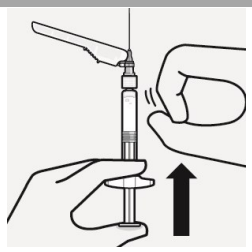


Resuspend microspheres
Fully remove the blister pouch.
Just before injection, shake syringe vigorously again, as some settling will have occurred.

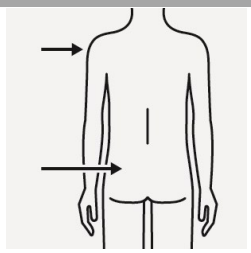
Step 4	Inject dose



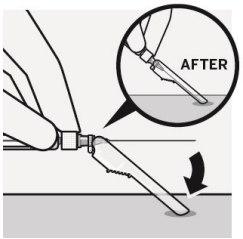
Remove transparent needle protector
Move the needle safety device back towards the syringe,
as shown. Then hold white collar



Remove air bubbles
Hold syringe upright and tap gently to make any air bubbles rise to the top. Slowly and carefully press



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



Secure needle in safety device
Using <u>one hand</u>, place needle safety device at a 45 degree angle on a hard, flat surface. Press down with a firm,

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

on syringe and carefully pull the transparent needle protector straight off. **Do not** twist transparent needle protector, as the luer connection may loosen.	plunger rod upward to remove air.	Gluteal injection should be made into the upper-outer quadrant of the gluteal area. **Do not administer intravenously.**	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.	Also discard the unused needle provided in the dose pack.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

Reconstitution:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
12.5 mg			
5 mL	2 mL	2 mL	6.25 mg/mL
25 mg			
5 mL	2 mL	2 mL	12.5 mg/mL
37.5 mg			
5 mL	2 mL	2 mL	18.75 mg/mL
50 mg			
5 mL	2 mL	2 mL	25 mg/mL

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Human Experience

No cases of overdose were reported in premarketing studies with RISPERDAL CONSTA®. Because RISPERDAL CONSTA® is to be administered by healthcare professionals, the potential for overdosage by patients is low.

Cases of overdose have been reported with oral RISPERDAL®; the estimated doses were between 20 and 360 mg. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, namely drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation, widened QRS complex, convulsions, hyponatremia and hypokalemia were also reported. Torsade de pointes has been reported in association with combined overdose of oral RISPERDAL® and paroxetine.

Treatment of Overdosage

In case of acute overdosage, establish and maintain an airway to ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to RISPERDAL CONSTA®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Risperidone, a benzisoxazole derivative, is a novel antipsychotic drug which binds with high affinity to serotonin type 2 (5-HT_2), dopamine type 2 (D_2), and α_1-adrenergic receptors. Risperidone binds with a lower affinity to the α_2-adrenergic and histamine H_1 receptors. Risperidone does not bind to dopamine D_1 receptors and has no affinity (when tested at concentrations > 10^{-5} M) for muscarinic cholinergic receptors. Due to the lack of muscarinic receptor binding, risperidone is not expected to produce anticholinergic adverse effects.

Receptor occupancy was also demonstrated in vivo in humans. Using positron emission tomography, risperidone was shown to block both 5-HT_{2A} and dopamine D_2 receptors in three

healthy volunteers. Although risperidone is a potent D_2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy in animal models than classical antipsychotics. Risperidone has also been found to be one of the most potent known antagonists of 5-HT_{2A} (cloned human receptor); 5-HT_{2A} antagonism has been shown to reverse deficits in several in vivo animal models predictive of novel antipsychotic activity (PCP-induced social deficit, microdialysis assessment of dopamine output in prefrontal cortex, glutamate antagonist-induced hyperlocomotion). Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study of a single, 1 mg oral dose of ^{14}C-risperidone administered as solution to three healthy male volunteers. Total recovery of radioactivity at 1 week was 84%, including 70% in urine and 14% in feces.

Absorption: After a single intramuscular injection of RISPERDAL CONSTA®, there is a small initial release of the drug (< 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug starts from week 3 onward, is maintained from 4 to 6 weeks, and subsides by 7 weeks following the intramuscular (IM) injection. Therefore, oral antipsychotic supplementation should be given during the first 3 weeks of treatment with RISPERDAL CONSTA® to maintain therapeutic levels until the main release of risperidone from the injection site has begun (see **DOSAGE AND ADMINISTRATION**). Following single doses of RISPERDAL CONSTA®, the pharmacokinetics of risperidone, 9-hydroxyrisperidone (the major metabolite), and risperidone plus 9-hydroxyrisperidone were linear in the dosing range of 12.5 mg to 50 mg.

The combination of the release profile and the dosage regimen (IM injections every 2 weeks) of RISPERDAL CONSTA® results in sustained therapeutic concentrations. Steady-state plasma concentrations are reached after 4 injections and are maintained for 4 to 6 weeks after the last injection. Following multiple doses of 25 mg to 50 mg RISPERDAL CONSTA®, plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are linear. The half-life of risperidone plus 9-hydroxyrisperidone is 3 to 6 days, and is associated with a monoexponential decline in plasma concentrations. This half-life of 3 to 6 days is related to the erosion of the microspheres and subsequent absorption of risperidone. The elimination phase is complete approximately 7 to 8 weeks after the last injection.

After repeated IM injections of 25 mg or 50 mg RISPERDAL CONSTA® every 2 weeks, median trough and peak plasma concentrations of risperidone plus 9-hydroxyrisperidone fluctuated between 9.9 ng/mL to 19.2 ng/mL and 17.9 ng/mL to 45.5 ng/mL, respectively. Fluctuations in plasma concentrations were lower with RISPERDAL CONSTA® than with risperidone oral tablets. Median C_{max}/C_{min} ratios for risperidone were approximately 2 after IM injection and 20–30 after oral intake; median C_{max}/C_{min} ratios for risperidone plus 9-hydroxyrisperidone were approximately 2 after IM injection and 3–4 after oral intake.

Gluteal and deltoid intramuscular injections at the same doses are bioequivalent and, therefore, interchangeable.

Distribution: Once absorbed, risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is approximately 88%, and that of 9-hydroxyrisperidone is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites.

Metabolism: Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, cytochrome $P_{450}IID_6$ (CYP 2D6). A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity to risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. The hydroxylation of risperidone is dependent upon debrisoquine 4-hydroxylase, i.e., the metabolism of risperidone is sensitive to debrisoquine hydroxylation type genetic polymorphism. Consequently, the concentrations of parent drug and active metabolite differ substantially in extensive and poor metabolizers. However, the concentration of risperidone and 9-hydroxyrisperidone combined did not differ substantially between extensive and poor metabolizers, and elimination half-lives were similar in all subjects (approximately 20 to 24 hours).

Excretion: The clearance of risperidone and risperidone plus 9-hydroxyrisperidone was 13.7 L/h and 5.0 L/h in extensive CYP 2D6 metabolizers, and 3.3 L/h and 3.2 L/h in poor CYP 2D6 metabolizers, respectively. No accumulation of risperidone was observed during long-term use (up to 12 months) in patients treated every 2 weeks with 25 mg or 50 mg of RISPERDAL CONSTA®.

Special Populations and Conditions

Pediatrics: No data available.

Geriatrics: In an open-label trial, steady-state concentrations of risperidone plus 9-hydroxyrisperidone in otherwise healthy elderly patients (≥ 65 years old) treated with risperidone powder for injectable prolonged-release suspension for up to 12 months fell within the range of values observed in otherwise healthy nonelderly patients. For these reasons, dosing recommendations are the same for otherwise healthy elderly patients and nonelderly patients (see **DOSAGE AND ADMINISTRATION**).

Gender: No specific pharmacokinetic study was conducted to investigate gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (with or without correction for body weight).

Race: No specific pharmacokinetic study was conducted to investigate race effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to race.

Hepatic Insufficiency: Whereas the pharmacokinetics of oral risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin

and α_1-acid glycoprotein. Although patients with hepatic impairment were not studied with risperidone powder for injectable prolonged-release suspension, it is recommended that patients with hepatic impairment be carefully titrated on oral risperidone before treatment with RISPERDAL CONSTA® is initiated at a dose of 25 mg. Alternatively, a starting dose of 12.5 mg RISPERDAL CONSTA® may be appropriate (see **WARNINGS AND PRECAUTIONS — Hepatic/Biliary/Pancreatic** and **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency: In patients with moderate to severe renal disease treated with oral risperidone, clearance of risperidone and 9-hydroxyrisperidone combined was decreased by about 60%, C_{max} and AUC were increased by about 40% and 160% respectively, and half-life was prolonged by about 60% compared with young healthy subjects. Although patients with renal impairment were not studied with risperidone powder for injectable prolonged-release suspension, it is recommended that patients with renal impairment be carefully titrated on oral risperidone before treatment with RISPERDAL CONSTA® is initiated at a dose of 25 mg. Alternatively, a starting dose of 12.5 mg RISPERDAL CONSTA® may be appropriate (see **WARNINGS AND PRECAUTIONS — Renal** and **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

The entire kit should be stored in the refrigerator (2°C–8°C) and protected from light.

If refrigeration is unavailable, kit 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. Protect from light.

RISPERDAL CONSTA® must be suspended **only** in the diluent supplied in the dose pack. The entire volume of diluent (2 mL) must be used for suspension of the microspheres.

Upon suspension in the diluent, it is recommended to use RISPERDAL CONSTA® immediately. RISPERDAL CONSTA® must be used within 6 hours of suspension. Resuspension of RISPERDAL CONSTA® will be necessary prior to administration as settling will occur over time since the product is in suspension. Keeping the vial upright, shake vigorously for at least 10 seconds to resuspend the microspheres. Reconstituted product in syringe must be resuspended by shaking vigorously. Once in suspension, the product should not be exposed to temperatures above 25°C.

RISPERDAL CONSTA® should be kept out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

RISPERDAL CONSTA® is available in dosage strengths of 12.5, 25, 37.5, or 50 mg risperidone. It is provided as a kit, and includes a vial containing the risperidone microspheres, a prefilled syringe containing 2 mL of diluent for RISPERDAL CONSTA®, one West-Medimop Vial

Adaptor®, and two Terumo SurGuard®-3 Injection Needles for intramuscular injection (a 20G TW 2-inch needle for gluteal administration and a 21G UTW 1-inch needle for deltoid administration). The colour of the vial cap varies by dosage strength: violet (12.5 mg), pink (25 mg), green (37.5 mg), or blue (50 mg). The syringe barrel has a green band.

Composition

RISPERDAL CONSTA® is a combination of extended-release microspheres for injection and diluent for parenteral use.

The extended-release microspheres formulation is a white to off-white, free-flowing powder that is available in dosage strengths of 12.5, 25, 37.5, or 50 mg risperidone per vial. Risperidone is micro-encapsulated in 7525 polylactide-co-glycolide (PLG) at a concentration of 381 mg risperidone per gram of microspheres.

The diluent for parenteral use is a clear, colourless solution in a prefilled syringe. Composition of the diluent includes polysorbate 20, sodium carboxymethylcellulose, disodium hydrogen phosphate dihydrate, citric acid anhydrous, sodium chloride, sodium hydroxide, and water for injection.

The microspheres are suspended in the diluent prior to injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

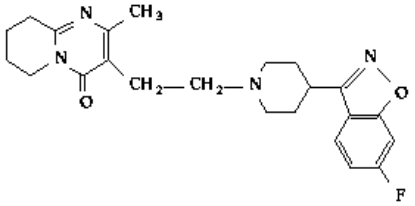
Drug Substance

Proper name: risperidone

Chemical name: 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one

Molecular formula and molecular mass: $C_{23}H_{27}FN_4O_2$, 410.49

Structural formula:



Physicochemical properties: Risperidone is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

Ionization Constant: $pKa_1 = 8.24$
$pKa_2 = 3.11$

Partition Coefficient: log P = 3.04

Melting Point: 169 - 173°C

CLINICAL TRIALS

Schizophrenia

The effectiveness of RISPERDAL CONSTA® (risperidone) powder for injectable prolonged-release suspension in the treatment of schizophrenia was established, in part, on the basis of extrapolation from the established effectiveness of the oral formulation of risperidone. In addition, the effectiveness of RISPERDAL CONSTA® in the treatment of schizophrenia was established in a 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia.

Efficacy data were obtained from 400 patients with schizophrenia who were randomized to receive injections of either 25, 50, or 75 mg RISPERDAL CONSTA® or placebo every 2 weeks.

During a 1-week run-in period, patients were discontinued from other antipsychotics and were titrated to a dose of 4 mg oral RISPERDAL®. Patients who received RISPERDAL CONSTA® were given doses of oral RISPERDAL® (2 mg for patients in the 25 mg group, 4 mg for patients in the 50 mg group, and 6 mg for patients in the 75 mg group) for the 3 weeks after the first injection to provide therapeutic plasma concentrations until the main release phase of risperidone from the injection site had begun. Patients who received placebo injections were given placebo tablets.

Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated, multi-item inventory composed of five subscales to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression.

The primary efficacy variable in this trial was change from baseline to endpoint in the total PANSS score. The mean total PANSS score at baseline for schizophrenic patients in this study was 81.5.

Total PANSS scores showed significant improvement in the change from baseline to endpoint in schizophrenic patients treated with each dose of RISPERDAL CONSTA® (25 mg, 50 mg, or 75 mg) compared with patients treated with placebo. While there were no statistically significant differences between the treatment effects for the three dose groups, the effect size for the 75 mg dose group was actually numerically less than that observed for the 50 mg dose group.

Subgroup analyses did not indicate any differences in treatment outcome as a function of age, race, or gender.

Maintenance Treatment in Bipolar I Disorder – Monotherapy
The effectiveness of RISPERDAL CONSTA® when administered as monotherapy for the maintenance treatment of bipolar I disorder was established in a multicenter, double-blind, placebo-controlled study of adult patients who met DSM-IV criteria for Bipolar Disorder Type I, and at time of screening were either experiencing an acute manic or mixed episode or were already stabilized on either risperidone or other anti-manic medications. Acutely ill patients and patients stabilized on other anti-manic medications initiated the study by receiving 3 weeks of open-label treatment with oral risperidone to control acute manic symptoms and to discontinue other anti-manic medications.

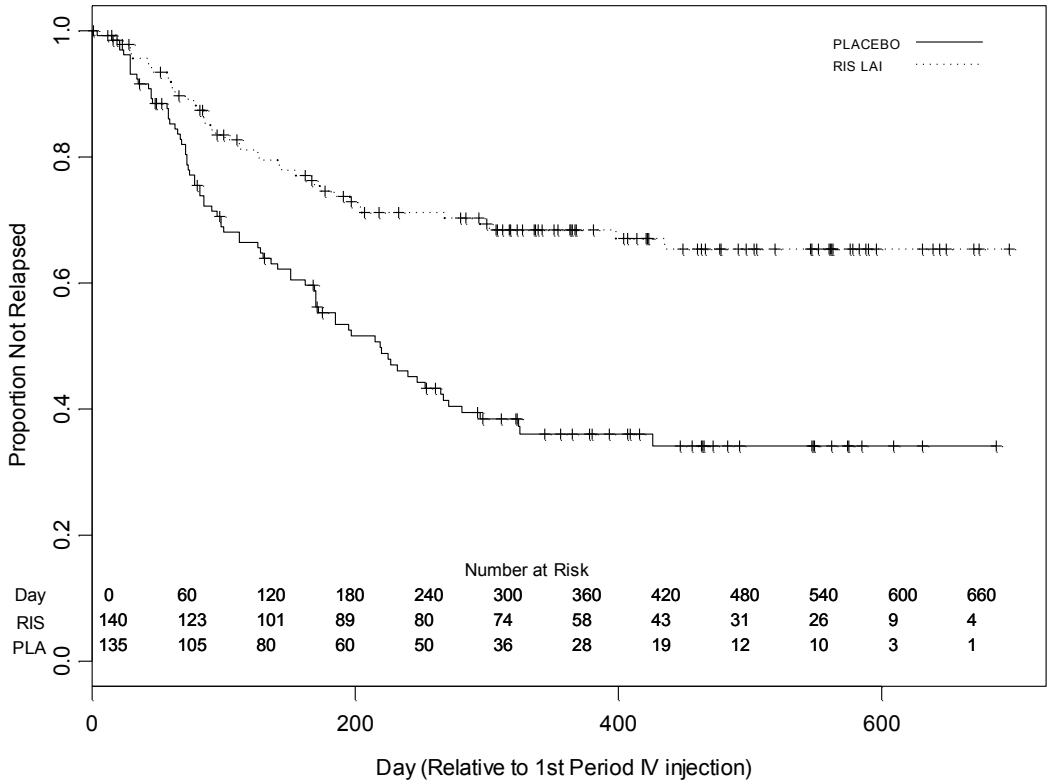
A total of 501 patients were treated during a 26-week open-label stabilization phase with RISPERDAL CONSTA® (starting dose of 25 mg, and titrated, if deemed clinically necessary, to 37.5 mg or 50 mg; for patients not tolerating the 25 mg dose, the dose could be reduced to 12.5 mg). For the 3 weeks after the first injection or after dose increases patients received supplementary doses of oral RISPERDAL® to provide therapeutic plasma concentrations until the main release phase of risperidone from the injection site had begun. In the open-label stabilization phase, 303 (60%) patients who received a stable dose of RISPERDAL CONSTA® for the last 8 weeks of the open-label phase and continued to meet the protocol-specified criteria for response were randomized to double-blind treatment with either the same dose of RISPERDAL CONSTA® or placebo injection. Non-response during the open label phase was defined by meeting any of the following criteria: met DSM-IV-TR criteria for manic, hypomanic,

mixed or depressed episode; needed treatment intervention with a mood stabilizer, antipsychotic, benzodiazepine, or antidepressant; required hospitalization for any bipolar mood episode; or had a YMRS total score > 12, a MADRS score > 12 or a CGI-S score > 4 at any single visit.

After randomization patients were monitored for relapse for up to 24-months. The primary endpoint was time to relapse to any mood episode (depression, mania, hypomania, or mixed) during double-blind treatment phase. Relapse during the double-blind phase was defined by meeting any of the same criteria used to define non-response during the open label phase or by the need for an increase in RISPERDAL CONSTA® dose, supplementation with oral risperidone, or addition of another antipsychotic or mood stabilizer. Secondary endpoints included the change in YMRS, MADRS and CGI-BP-S scores, from double-blind baseline to double-blind endpoint.

Time to relapse was delayed in patients receiving RISPERDAL CONSTA® monotherapy as compared to placebo ($p < 0.001$) (Figure 2.1). In the 24-month, double-blind phase, 30% of patients in the RISPERDAL CONSTA® group and 56% of patients in the placebo group relapsed. The majority of relapses were due to manic rather than depressive episodes. Based on their bipolar disorder history, subjects entering this study had, on average, more manic episodes than depressive episodes, and patients who entered the study during an acute episode were experiencing either manic or mixed episodes. Therefore, there are insufficient data to evaluate the effect of RISPERDAL CONSTA® with regard to the occurrence of depressive episodes in patients with bipolar I disorder. Secondary endpoints evaluating psychiatric symptoms severity, such as change in YMRS and CGI-S-BP during double-blind treatment, were consistent with the maintained treatment response that was observed with RISPERDAL CONSTA® compared to placebo.

Figure 2.1: Kaplan-Meier Curves of Time to Relapse During Double-Blind Treatment with RISPERDAL CONSTA®



Deltoid and Gluteal Administration
Deltoid injection has been shown to be bioequivalent to gluteal injection. In an 8-week clinical trial evaluating multiple dose tolerability of deltoid injections (n = 53), patients received up to 4 injections (up to 2 injections per arm at two week intervals) into the deltoid muscle.

DETAILED PHARMACOLOGY

Risperidone represents a new generation of neuroleptic drugs combining potent serotonin type 2 (5-HT_2) and dopamine-D_2 antagonism.

In in vitro receptor binding assays, risperidone exhibited high binding affinity for the following receptor sites (K_i nM): 5-HT_2 (0.16), α_1-adrenergic (0.81), dopamine-D_2 (1.4), H_1-histaminergic (2.1), and α_2-adrenergic (7.5). Risperidone was inactive at muscarinic cholinergic receptor sites (K_i: > 10,000 nM). Affinity for dopamine-D_2 binding sites in rat brain showed little regional variation and was comparable to the affinity for cloned human D_2 receptors.

Serotonin Antagonism
In rats, risperidone dose-dependently inhibited tryptamine-, mescaline-, 5-HTP-, and DOM (2,5-dimethoxy-4-methylamphetamine)-induced behavioural effects (ED_{50}: 0.014-0.049 mg/kg sc). Higher risperidone doses completely blocked the serotonin agonist-induced behavioural effects.

In drug discrimination studies, risperidone was a potent and selective antagonist of LSD and DOM (0.024-0.028 mg/kg sc), devoid of partial 5-HT_2 agonist activity and LSD-like abuse and dependence liability. Low doses of risperidone (0.01-0.16 mg/kg ip) increased deep slow wave sleep and decreased paradoxical sleep in rats.

Peripheral 5-HT_2 antagonism was reflected, at very low doses, in the antagonism of tryptamine-induced cyanosis in rats (ED_{50}: 0.0011 mg/kg sc) and serotonin-induced bronchospasm in guinea pigs (ED_{50}: 0.0027 mg/kg ip).

Dopamine-D_2 Antagonism

Risperidone dose-dependently antagonized apomorphine- and amphetamine-induced behavioural effects, namely apomorphine-induced climbing behaviour in mice (ED_{50}: 0.062 mg/kg ip), amphetamine-induced hyperactivity in rats (0.02-0.04 mg/kg), apomorphine-induced stereotypy in rats (ED_{50}: 3.2 mg/kg ip), and apomorphine-induced rotational behaviour in unilaterally 6-hydroxy-dopamine-lesioned mice (0.1-1.0 mg/kg dose range). Risperidone also reduced spontaneous locomotion (ED_{50}: 0.22 mg/kg sc) and conditioned avoidance responding (ED_{50}: 0.48 mg/kg ip) in rats and induced catalepsy in the 0.59-3.0 mg/kg (sc) dose range.

Risperidone increased the levels of the dopamine metabolites (DOPAC and HVA) in a dose-dependent manner in various brain regions.

In common with other neuroleptics, risperidone also produced effects that are related to blockade of peripheral dopamine-D_2 receptors. Risperidone was a potent antagonist of apomorphine-induced emesis in dogs (0.005-0.007 mg/kg following iv, sc, or po administration). After oral administration, the onset of action was rapid and the duration was 24 hours. In vitro, risperidone reversed dopamine-suppressed prolactin release in primary culture of rat anterior pituitary cells. In vivo, risperidone dose-dependently increased serum prolactin levels in rodents after single and repeated administration.

Combined 5-HT_2 and Dopamine-D_2 Antagonism

The combined 5-HT_2 and dopamine-D_2 antagonism of risperidone resulted in differences from specific dopamine-D_2 antagonists. Risperidone reduced both spontaneous and amphetamine-stimulated locomotor activity more gradually. Dopamine-D_2 receptor occupation and the extent of dopamine turnover potentiation varied according to brain region. Low doses of risperidone completely blocked 5-HTP-induced head twitches and discrimination stimulus effects of the hallucinogenic serotonin agonists DOM and LSD. Disinhibitory effects in amphetamine-treated rats were seen over a much wider dose range. Risperidone increased social interaction time. A sequential tryptamine-apomorphine challenge was more readily controlled.

Interaction with Histamine-H_1 and α-Adrenergic Receptors

Blockade of peripheral histamine-H_1 receptors by risperidone was evidenced by protection from compound 48/80-induced lethality in rats (ED_{50}: 0.014 mg/kg sc) although the very potent 5-HT_2 antagonism of risperidone might have contributed to this activity. Risperidone antagonized histamine-induced bronchospasm in guinea pigs (ED_{50}: 0.037 mg/kg ip).

Risperidone also blocked α_1-adrenoceptors as indicated by protection from norepinephrine-induced lethality in rats (ED_{50}: 0.074 mg/kg sc) and induction of palpebral ptosis (ED_{50}: 0.19 mg/kg sc).

Blockade of central α_2-adrenoceptors was found at 2.4 mg/kg in the xylazine test. Reversal of the antidiarrheal effect of clonidine at 0.67 mg/kg reflected blockade of peripheral α_2-adrenoceptors.

Cardiovascular effects, such as hypotension and reflex tachycardia observed in dogs, are considered to be predominantly consequences of vascular α_1-adrenoceptor blockade. These effects diminished or disappeared during chronic treatment, indicating the development of tachyphylaxis.

In anaesthetized mongrel dogs, risperidone produced dose-dependent vasodilation accompanied by an increase in cardiac contractility, aortic blood flow and cardiac output. The minimal effective dose (0.005 mg/kg) was similar to the antiemetic dose.

In conscious Labrador dogs, a single oral dose of 0.08 mg/kg (11 times the oral antiemetic dose) reduced systolic and diastolic pressure but did not affect heart rate. After a single oral dose of 0.31 mg/kg (44 times the oral antiemetic dose), the blood pressure lowering effect became more pronounced, heart rate increased and QTc interval became prolonged but PQ and QRS intervals remained essentially uninfluenced.

Drug Interactions

After repeated administration of oral doses up to 10 mg/kg/day, risperidone did not interact in vivo with liver drug-metabolizing enzymes (cytochrome P-450, glucuronosyltransferase, and cytochrome c-reductase) that are known to be generally involved in the metabolism of drugs.

Pharmacology of the 9-Hydroxy Metabolite

Risperidone is predominantly metabolized to its 9-hydroxy derivative. This metabolite and its 2 enantiomers were comparable in potency, onset and duration of action, oral activity and pharmacological profile to risperidone.

Pharmacokinetics

Following single intramuscular injection of risperidone powder for injectable prolonged-release suspension in dogs, the typical profile of the plasma concentration of risperidone and 9-hydroxyrisperidone combined versus time consisted of three distinct phases. In the first phase, a peak was observed in the first days following injection that resulted from diffusion-controlled release of the risperidone from the microspheres. During the second phase, which started post-peak in the first phase and lasted up to day 18-21 post-injection, plasma concentrations remained low and this resulted in a lag phase in the profile with little drug being released. The main release of the risperidone occurred during the third phase that lasted 2 to 3 weeks.

In rats the plasma concentrations of risperidone and 9-hydroxyrisperidone combined following subcutaneous and intramuscular injection were comparable between males and females. Steady-state was achieved within 4 injections once every 2 weeks at the same dose level. Subcutaneous

and intramuscular injection of the risperidone powder for injectable prolonged-release suspension in rats produced a fairly comparable exposure although somewhat higher following subcutaneous injection because of a larger initial peak.

In dogs, the applied dose range produced a fairly dose-proportional increase in AUC values. Steady-state was achieved within the fourth consecutive injection at the same dose level. At steady-state, the fluctuations in the plasma concentration-time profile, following administration every 2 weeks, were low. The peak to plasma concentration ratio was on average 1.6.

TOXICOLOGY

Acute Toxicity

The LD_{50} values for risperidone, 14 days after administration were as follows:

Table 2.1: LD_{50} values for risperidone 14 days after administration

Route	Species	Number and Sex of Animals	LD_{50} in mg/kg (limits)
ORAL	Mice	90M	82 (73-92)
		90F	63 (56-71)
	Rats	60M	113 (82-157)
		60F	57 (39-83)
	Dogs	32M&F	18 (14-24)
		2M	> 10
INTRAVENOUS	Mice	60M	30 (26-33)
		70F	27 (23-31)
	Rats	70M	34 (31-38)
		70F	35 (32-39)
	Dogs	20M	14 (11-18)
		20F	18 (14-24)
SUBCUTANEOUS	Rats	60M	172 (132-225)
		60F	98 (59-162)

Toxicity was manifested by symptoms such as palpebral ptosis, prostration, catalepsy, sedation, hypothermia, and hypotonia at all doses, and clonic convulsions and loss of righting reflex at near lethal and lethal doses. Occasionally, signs of gastrointestinal disturbance were present. Autopsy occasionally revealed gastric lesions and bleeding in rodents. All survivors recovered within the 14-day observation period.

The acute oral toxicity of 9-hydroxyrisperidone in rats was similar to that of the parent drug.

REPEAT-DOSE TOXICITY IN WISTAR RATS

Subcutaneous - 6-Month Pilot Toxicity Study

Risperidone powder for injectable prolonged-release suspension was administered subcutaneously once a month for 6 months to 5 male and 5 female rats per dosage group in order to determine the potential toxicity. Initially, the doses were 10, 40, and 80 mg/kg. Since the high dose was very well tolerated, all doses were increased from the second administration onwards to 20, 80, and 160 mg/kg to elicit toxicological effects. For the last administration, doses were again increased to 80, 320, and 640 mg/kg. No test article-related mortality occurred during the course of the study.

A dose of 10 mg/kg did not result in risperidone-related adverse effects, except for some slight sedation, which was noted in the first week after dosing. At 20 and 40 mg/kg, sedation was observed in the first weeks after dosing. When rats were dosed at 80, 160, 320, and 640 mg/kg, the degree and duration of sedation increased dose-dependently. In the low-dosed group (up to 80 mg/kg), slight increases in body weight and food consumption, especially in females, were present, while dosing at 320 and 640 mg/kg resulted in decreases in body weight and food consumption, especially in males.

At autopsy, swollen pituitary glands in both sexes and stimulation of the mammary glands in females were observed in all dosage groups. Furthermore, stimulation of the mammary gland was present in one male dosed at 640 mg/kg. Skin irritation at the injection site was seen in one rat dosed at 80 mg/kg and in one rat dosed at 160 mg/kg, and a chronic foreign body reaction was found at the administration sites of nearly all animals of each dosage group.

Subcutaneous - 6-Month Toxicity Studies

Twenty male and 20 female Wistar rats per dosage group were dosed for 6 months with risperidone powder for injectable prolonged-release suspension administered subcutaneously once a month. The selected doses were 80, 160, and 640 mg/kg given at a volume ranging from 0.4 to 1.6 mL/100 g body weight. Lower doses of 20, 40, and 160 mg/kg were given during the first 2 months, followed by a third administration of 40, 80, and 320 mg/kg and finally reached the doses of 80, 160, and 640 mg/kg (4th to 6th administration).

No treatment-related mortality occurred during the study up to a dose of 80 mg/kg. From a dose of 160 mg/kg onwards, deaths occurred in both sexes.

At autopsy, the increased weight of the adrenals in males was considered as test article-related. No macroscopical changes were seen in males, whilst in females, stimulation of the mammary glands was evidenced in all dosage groups.

Histologically, prolactin-mediated changes were found in the prostate, mammary glands, female genital tract, and hypophysis in all test article-dosed males and females. Also, swelling of cortical cells in the adrenal cortex was observed in all test article-dosed males. Encapsulation and a giant cell reaction at the administration site were considered related to the administration of microspheres.

In a second six-month toxicity study, Wistar rats were dosed with risperidone powder for injectable prolonged-release suspension every two weeks by the subcutaneous route. The doses were gradually increased over time in the different dosage groups. The first doses were 10, 20, and 40 mg/kg, the following two doses were 20, 40, and 80 mg/kg followed by the doses of 40, 80, and 160 mg/kg at volumes of 0.1, 0.2, and 0.4 mL/100 g body weight, respectively, from the fifth administration onwards. No test article-related mortality and no ocular changes were present in any of the dosage groups.

Changes in blood, serum and urine parameters were present in all dosage groups. An increase in the weight of the spleen and a decrease in the weight of the thymus in both sexes, and an increase in the weight of the adrenals and a decrease in the weight of the testes in males were present in all dosage groups. A decrease in the weight of the ovaries was seen in females at doses of 80 and 160 mg/kg. Changes in the prostate (grey and swollen) and swollen adrenal glands in males, and mammary gland stimulation, small ovaries, and a small uterus in females were observed in animals of all dosage groups.

Histological examination revealed prolactin-mediated effects in the pituitary gland, dorsolateral and ventral prostate, coagulating glands and seminal vesicles, mammary glands in both sexes and in the female genital tract in all dosage groups.

At the administration site, a powdery deposit with histologically a chronic inflammatory fibro-granulomatous reaction, related to the administration of the depot suspension, was present in the vehicle and all test article-dosed groups.

Intramuscular - 12-Month Toxicity Study

Risperidone powder for injectable prolonged-release suspension was administered every two weeks intramuscularly to SPF Wistar rats (20 males and 20 females per group) at dosages of 5 and 40 mg/kg body weight for a period of 12 months. The control group was injected with NaCl 0.9%. The volumes injected were 0.08 mL/100 g body weight (or 0.3 mL/site) for the vehicle, control and high-dosage group and 0.01 mL/100 g body weight (or 0.04 mL/site) for the low-dosage group. No test article-related mortality was seen after twelve months of dosing. In the vehicle group, decreases in white blood cells, lymphocytes, and aspartate aminotransferase in females, and a decrease in alkaline phosphatase in males were seen.

A decrease in the weight of the testes in males, and an increase in the weight of the liver and decreases in the weight of the thymus and ovaries in females were present at a dose of 5 mg/kg body weight. At a dose of 40 mg/kg body weight, aldosterone was decreased in both sexes and there was an increase in the weight of the kidneys and adrenals and a decrease in the weight of gonads in both sexes. An increase in the weight of the spleen in males, and an increase in the weight of the liver and decrease in the weight of the thymus in females were noted.

At autopsy, macroscopical changes from a dose of 5 mg/kg onwards were pale kidneys in both sexes. At a dose of 40 mg/kg body weight, swollen adrenal glands in both sexes, and a swollen pituitary gland and prostate changes in males were present.

Histologically, prolactin-mediated changes were evidenced from a dose of 5 mg/kg body weight onwards in the coagulating glands, seminal vesicles, prostate, pituitary gland, mammary gland, and female genital tract. Changes in the adrenals and signs of osteodystrophy were seen in both sexes at a dose of 40 mg/kg body weight.

A powdery deposit at the administration site and, histologically, chronic inflammatory changes at the injection site, minimal granulomatous foci in the lungs, and an activation of the mononuclear phagocyte system were seen in the vehicle group and each test article-dosed group.

A slight increase in necrosis with cellular debris and muscular degeneration at the administration site, due to the irritation of the test article, was present in the 40 mg/kg-dosed groups.

Repeated-Dose Toxicity in Beagle Dogs

Intramuscular - 6-Month Pilot Toxicity Study

In this pilot study, Beagle dogs were administered with risperidone powder for injectable prolonged-release suspension every month. This study aimed to find adequate doses for a full 6-month study. Initially, the doses were set at 0.63, 2.5, and 10 mg/kg (0.2 mL/kg). Since no significant signs of toxicity were observed during the first month, all doses were increased from the second administration onwards to 5, 10, and 20 mg/kg (0.2 mL/kg). For the last administration, doses were again increased to 20, 40, and 80 mg/kg (0.4 mL/kg). Each dosage group consisted of 2 male and 2 female dogs. Risperidone, as a depot formulation, was very well tolerated in dogs and did not result in mortality after 6 months of dosing. No test article-related effects on ECG, heart rate, blood pressure, blood, serum, and urine analysis were seen up to the highest dose of 80 mg/kg in any dog. No visible reactions at the administration sites were observed.

Intramuscular - 6-Month Toxicity Study

Based on the results of the pilot study and human kinetic data, doses selected for this study were 10 mg/kg for the low dose (steady-state plasma levels were in the range of the therapeutic plasma levels in humans) and 80 mg/kg as the high dose (steady-state levels were approximately 20 times higher than the therapeutic plasma levels in men), administered to Beagle dogs once a month. However, since sedation in the animals would be too severe when these doses would be given from the first administration onwards, it was decided to start at lower doses, i.e. 2.5, 5, and 20 mg/kg followed by doses of 5, 10, and 20 mg/kg and 10, 20, and 40 mg/kg for the second and third administrations, respectively, to finally reach the intended doses of 10, 20, and 80 mg/kg.

All dogs survived the study. Also, no clinical abnormalities, ocular changes nor any effects on heart rate and ECG were noted in any dosage group. Test article-related changes were seen in blood (decreases in white blood cells and thrombocytes), serum (increase in glucose), and urine parameters (decrease in pH) from the dose of 10 mg/kg onwards.

At autopsy, increased spleen weights were noticed in all dosage groups. Additionally, increased pancreas weights and decreased prostate weights were seen in the high dosage group dosed up to 80 mg/kg.

Histological examination revealed changes in the female genital tract. There were also changes in the male genital tract, which included a reduced glandular development of the prostate in males of the high-dosage group. Also, an increase in accumulation of red blood cells in the red pulp of the spleen in both sexes was seen in all dosage groups. The changes in the female genital tract and prostate were determined as prolactin-mediated changes, while the increase in accumulation of red blood cells in the spleen was a consequence of the α-lytic effect of risperidone.

Intramuscular - 12-Month Toxicity Study

In a chronic 12-month toxicity study, risperidone powder for injectable prolonged-release suspension was administered every two weeks intramuscularly to Beagle dogs. The first two doses for the low-, medium-, and high-dosage group were 1.25, 2.5, and 5 mg/kg followed by two administrations of 2.5, 5, and 10 mg/kg and finally reached the doses of 5, 10, and 20 mg/kg from the fifth dosage onwards till the end of the study.

No mortality and no changes in ECG and heart rate, no eye changes and no effects on body weight, food consumption, and urinary parameters were observed in any of the dosage groups. A transient sedation on the day of dosing was present from a dose of 2.5 mg/kg onwards. The animals adapted to this pharmacological effect since sedation was no longer seen from the second dose of 5, 10, and 20 mg/kg in the low, medium and high dose respectively. A vaginal discharge was absent in nearly all animals and white blood cells, neutrophils, and lymphocytes were decreased from a dose of 2.5 mg/kg onwards.

At autopsy, the weight of the spleen was increased and the weight of the prostate was slightly decreased in all dosage groups and the weight of the testes was decreased at 20 mg/kg. Prolactin-mediated effects in the prostate (atrophy), female mammary glands (stimulation), female genital tract (resting appearance), and pituitary gland (increase in the number of prolactin-immuno reactive cells), and an increase in accumulation of red blood cells in the red pulp of the spleen (α-lytic effect) were seen in all dosage groups.

Summary

Both in rats and dogs, chronic dosing up to 12 months of risperidone powder for injectable prolonged-release suspension did not result in unexpected risperidone-related findings when compared to the oral risperidone toxicity studies. The findings were mainly the result of prolactin-mediated effects, (α-lytic effects) or they were related to exaggerated pharmacological effects of risperidone.

In addition, a powdery deposit, histologically evidenced as encapsulation of the microspheres, and an inflammatory reaction at the administration site, after either subcutaneous or intramuscular administration, were found in all groups, including the vehicle group. This was considered to be related to the gradual biodegradation of the microspheres.

No no-toxic-effect doses could be established in both species.

Local Tolerance Studies

Several single-dose tolerance studies were performed in dogs, pigs, or rats, in order to examine the local reaction at the administration site and/or systemic reaction after injection of risperidone microspheres. Both in dogs and pigs, the animals treated with risperidone powder for injectable prolonged-release suspension intramuscularly showed irritation at the injection site, which was evidenced by clinical observations, increases in creatine kinase, and/or histopathological findings (fibro-granulomatous reactions and giant cells with granulocytic infiltration). No systemic reaction was seen in either species.

Mechanistic Studies

Supportive mechanistic studies were performed in dogs to explain the early release noted in some patients in early clinical studies. Several studies were designed mainly to test two effects, i.e. local inflammation and allergy/anaphylactic reaction, which could result in faster release of risperidone out of the microspheres. A dog model was chosen as a worst case model. The dog appeared to be more sensitive than humans to an early release of risperidone from the microspheres. Moreover, this phenomenon was seen neither in rats nor in pigs. Possible influencing factors, including volume, mass, or concentration of risperidone, repeated injections at the same site, and different diluents, were studied. The results of the different studies showed that a local inflammation, probably worsened by degradation of polysorbate 20, which is present in the diluents, could explain the observed phenomena.

Carcinogenicity

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats in which risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis, or 0.2, 0.75, and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas.

Risperidone powder for injectable prolonged-release suspension was evaluated in a 24-month carcinogenicity study in which SPF Wistar (Hannover) rats were treated every 2 weeks with IM injections of either 5 mg/kg or 40 mg/kg. These doses are equivalent to 0.97 to 7.8 times the maximum human dose (50 mg) on a mg/m^2 basis. A control group received injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres.

There was a significant increase in pituitary gland adenomas, endocrine pancreas adenomas, and adrenomedullary pheochromocytomas at 8 times the IM maximum recommended human dose (MRHD) on a mg/m^2 basis. Hypercalcemia, reported to contribute to an increased incidence of adrenal medullary tumours, was observed in both groups. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 8 times the IM MRHD on a mg/m^2 basis). A significant increase in renal tubular tumours (adenomas, adenocarcinomas) was observed in male rats at 8 times the IM MRHD on a mg/m^2 basis. Plasma exposures (AUC) in rats were 0.3 and 2 times (at 5 and 40 mg/kg, respectively) the expected

plasma exposure (AUC) at the IM MRHD. At a dose of 40 mg/kg, changes were additionally seen in the bones (osteodystrophy) in both sexes.

Dopamine D_2-antagonists have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies of oral risperidone; however, measurements taken during the subchronic toxicity studies showed that oral risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the oral carcinogenicity studies. Serum prolactin levels increased in a dose-dependent manner up to 6- to 1.5-fold in male and female rats, respectively, at the end of the 24-month treatment with risperidone powder for injectable prolonged-release suspension every 2 weeks. Increases in the incidence of pituitary gland, endocrine pancreas, and mammary gland neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and may be prolactin-mediated.

The mechanism underlying the renal tumours in male Wistar (Hannover) rats treated with RISPERDAL CONSTA® is unknown. A treatment-related increase in renal tumour incidence did not occur in the oral carcinogenicity study 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 for human risk of the findings of prolactin-mediated tumours and of the presumed rat substrain-specific renal tumours is unknown.

No increased incidence of injection-site tumours was seen in the microspheres vehicle group. There was no increase in tumour incidence at the administration site.

Reproductive and Developmental Toxicology

A Segment II study was conducted in Sprague-Dawley rats. Groups of 24 female rats received a single IM dose of risperidone powder for injectable prolonged-release suspension at a total body dose of 10 or 20 mg/kg body weight, saline or vehicle. In addition, one group received risperidone 2.5 mg/kg body weight/day by gavage from Day 6 through Day 17 of pregnancy and served as an oral reference group. There was no drug-related mortality.

There were no relevant drug-related effects on pregnancy or litter parameters. No relevant fetal abnormalities were seen in any dosage group.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to risperidone therapy is unknown (see **WARNINGS AND PRECAUTIONS - Special Populations**).

In a toxicity study in juvenile rats treated with oral risperidone (0, 0.04, 0.16, 0.63 or 2.5/1.25

mg/kg/day), increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs treated with oral risperidone (0. 0.31, 1.25 or 5 mg/kg/day), 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 (1.5 mg/day); while effects on long bones and sexual maturation were observed at 15 times the maximum human oral exposure in adolescents.

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PART III: CONSUMER INFORMATION

PrRISPERDAL CONSTA®
risperidone powder for Injectable Prolonged-Release Suspension

This leaflet is Part III of a three-part "Product Monograph" published when RISPERDAL CONSTA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RISPERDAL CONSTA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
RISPERDAL CONSTA® belongs to a group of medicines called antipsychotic drugs.

RISPERDAL CONSTA® is used to treat the symptoms of schizophrenia and related psychotic disorders, as well as those of bipolar disorder.

Signs and symptoms of schizophrenia, include but are not limited to hallucinations (hearing or seeing things that are not there), delusions, unusual suspiciousness, or emotional withdrawal. Patients suffering from schizophrenia may also feel depressed, anxious or tense.

Signs and symptoms of bipolar mania include but are not limited to: high, elevated or irritable mood, feeling invincible or all powerful, inflated self-esteem, racing thoughts, easily losing your train of thought, overreaction to what you see or hear, misinterpretation of events, speeded-up activity, talking very quickly, talking too loudly, or talking more than usual, decreased need for sleep and poor judgment.

The doctor has prescribed RISPERDAL CONSTA®, to help relieve the symptoms that are bothering you/the patient you are caring for. Although RISPERDAL CONSTA® cannot cure the illness, it can keep the symptoms under control and reduce the risk of relapse as you/the patient you are caring for continue treatment.

What it does:
Antipsychotic medications affect the chemicals that allow communication between nerve cells (neurotransmitters). These chemicals are called dopamine and serotonin. Exactly how RISPERDAL CONSTA® works is unknown. However, it seems to readjust the balance of dopamine and serotonin.

When it should not be used:
RISPERDAL CONSTA® should not be given if an allergic reaction to risperidone, paliperidone, or any of the nonmedicinal ingredients of the product has occurred.

Symptoms of an allergic reaction may include: itching, skin rash, swelling of the face, lips or tongue, shortness of breath. **If you experience any of these symptoms/if these symptoms are experienced by the patient you are caring for, your doctor/the treating physician should be contacted immediately.**

The safety and efficacy of RISPERDAL CONSTA® in children under the age of 18 have not been established.

What the medicinal ingredient is:
risperidone

What the nonmedicinal ingredients are:
The diluent contains polysorbate 20, sodium carboxymethylcellulose, disodium hydrogen phosphate dihydrate, citric acid anhydrous, sodium chloride, sodium hydroxide, and water for injection.

Risperidone is micro-encapsulated in a polylactide-co-glycolide.

What dosage forms it comes in:
RISPERDAL CONSTA® is available in 4 strengths, 12.5 mg (violet cap), 25 mg (pink cap), 37.5 mg (green cap) and 50 mg (blue cap) per vial.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Increased Risk of Death in Elderly People with Dementia. Medicines like RISPERDAL CONSTA® can raise the risk of death in elderly people who have dementia. RISPERDAL CONSTA® is not approved for use in patients with dementia.

BEFORE starting RISPERDAL CONSTA® treatment, talk to your doctor if you/the patient you are caring for:

- have had serious allergic reactions to other medications, including oral risperidone or oral paliperidone. Even if you have not had a reaction to oral risperidone or oral paliperidone before, it can occur very rarely after receiving injections of RISPERDAL CONSTA®
- have a history of stroke, mini-strokes, high cholesterol or high blood pressure. Medicines like RISPERDAL CONSTA® can raise the risk of stroke in elderly people who have dementia. RISPERDAL CONSTA® is not approved for use in patients with dementia
- have had neuroleptic malignant syndrome (a disorder that causes you to have high fever and stiffness in your muscles)

- have had tardive dyskinesia (a disorder that causes you to have uncontrolled and repeated movements of the tongue, face or other body parts)
- have or are at risk for diabetes or high blood sugar or a family history of diabetes
- are pregnant, think you may be pregnant or planning to become pregnant
- are breast-feeding or planning to breast-feed
- have or have had prolonged and/or painful erection
- have or have ever had blackouts or seizures
- have a history of kidney or liver problems
- have a history of:
  - problems with the heart and/or blood vessels
  - any problems with the way your heart beats
- are being treated for high blood pressure
- are taking any medications that affect how your heart beats
- have had low white blood cell counts in your blood. Let your doctor know right away if you develop a fever or infection while being treated with RISPERDAL CONSTA®
- have high levels of cholesterol or fats (triglycerides) in your blood
- have, have a history of, or are at risk of:
  - sleep apnea (a sleep disorder where your breathing is interrupted during sleep)
  - sleep walking
  - sleep-related eating disorder
- are prone to hypotension (low blood pressure), have or have had a heart disease or heart disease treatment that makes you more likely to have low blood pressure or feeling dizzy or faint when you stand up from lying or sitting positions
- are at risk for developing blood clots. Risk factors include:
  - a family history of blood clots
  - being over the age of 65
  - smoking
  - being overweight
  - having a recent major surgery (such as hip or knee replacement)
  - not being able to move due to air travel or other reasons
  - taking oral birth control ("The Pill")
- have Parkinson's disease
- have Lewy body dementia
- have or have had breast cancer
- have pituitary tumours
- suffer from Alzheimer's disease
- are feeling thirsty and unwell
- exercise strenuously. This kind of medication may interfere with your body's ability to adjust to heat. You should avoid becoming overheated or dehydrated (for example with vigorous exercise or exposure to extreme heat) while taking RISPERDAL CONSTA®
- are taking any other medicines (prescription or over-the-counter medicines, or natural health products)
- drink alcoholic beverages or use drugs
- are planning to have an operation on the eye(s). During surgery to treat the cloudiness of the lens in your eye(s) (known as cataract surgery):
  - the pupil (the black circle in the middle of your eye) may not increase in size as needed
  - the iris (the coloured part of the eye) may become floppy during surgery. This may lead to eye damage

  Tell your eye doctor you are taking this medicine.

Elderly Patients with Dementia

- Studies in elderly patients with dementia have shown that -RISPERDAL® taken by itself or with furosemide (a "water pill") is associated with a higher rate of death **(see Serious Warnings and Precautions Box).**

  Tell your doctor if you are taking furosemide. This drug can be used to treat:
  - high blood pressure
  - some heart problems
  - swelling of parts of the body caused by the build-up of too much fluid.

- In elderly patients with dementia:
  - a sudden change in mental state
  - sudden weakness or numbness of the face, arms or legs, especially on one side of the body
  - slurred speech
  - vision problems

  have been seen.

  If any of these should occur, even for a short period of time, seek medical attention right away.

If you are taking blood pressure medication

Low blood pressure can result from using RISPERDAL CONSTA® together with medications used to treat high blood pressure. If you need to use both RISPERDAL CONSTA® and medications used to reduce blood pressure, consult your doctor.

Effects on newborns

You should not take RISPERDAL CONSTA® while you are pregnant or if you are planning on becoming pregnant unless you have talked to your doctor about it.

If you took RISPERDAL CONSTA® at any time while you were pregnant or if you took it before you became pregnant, the following symptoms may happen in your newborn baby:

- shaking
- stiffness in their muscles and/or weakness
- sleepiness
- agitation

- breathing problems
- difficulty feeding

Get medical help right away if your newborn baby has any of these symptoms.

In some cases, babies born to a mother taking risperidone during pregnancy have experienced symptoms that are severe and require the newborn to be hospitalized.

Other cautions
Driving and using machines: Do not drive or operate machinery until you know how you respond to RISPERDAL CONSTA®. Some people experience drowsiness or blurred vision while taking RISPERDAL CONSTA®.

Falls: Feeling sleepy, a fall in blood pressure when you stand up from sitting or lying down, vision and speech problems have been reported with the use of antipsychotic drugs. This can lead to falls that may cause fractures or other fall-related injuries. Certain medications, diseases or conditions can make this worse.

Weight gain: Weight gain has been seen in patients who are taking antipsychotic drugs. Your doctor may monitor your body weight when you are taking RISPERDAL CONSTA®.

Blood tests: Your doctor should do blood tests before you start taking RISPERDAL CONSTA®. They will check your blood sugar levels, and for those with certain risk factors, the level of white blood cells in your blood. Your doctor should continue to check your blood for as long as you are being treated with RISPERDAL CONSTA®.

It is important for the doctor to have all the above information before prescribing treatment and dosage. This list should be carefully reviewed by you/the caregiver and discussed with the doctor.

INTERACTIONS WITH THIS MEDICATION

Inform all doctors, dentists and pharmacists who are treating you that you are being treated with RISPERDAL CONSTA®.

Inform them if you are taking or are planning to take any other medicine, including other prescription or over-the-counter medications and natural health products. They will tell you which medicines you can take with RISPERDAL CONSTA®.

RISPERDAL CONSTA® can increase the effect of alcohol and medicines that reduce the ability to react ("tranquilizers", narcotic painkillers, certain antihistamines, certain antidepressants). It is recommended that you DO NOT drink alcohol when you are taking RISPERDAL CONSTA®. You should only take these other medicines when they have been prescribed by your doctor.

Some medicines, when they are taken together with RISPERDAL®, may increase or decrease the level of RISPERDAL® in your blood. Therefore, tell your doctor if you start and/or stop taking any of the below medicines, since your doctor may need to change the dose:

- Dopamine agonists, e.g., levodopa (a drug used to treat Parkinson's disease), as these may decrease the effect of RISPERDAL CONSTA®. Also RISPERDAL CONSTA® can affect how drugs used to treat Parkinson's disease work.

- Phenothiazines and some heart medications (e.g., medication for high blood pressure, antiarrhythmics, or beta-blockers), as these may interact with RISPERDAL CONSTA® to cause your blood pressure to drop too low.

- RISPERDAL CONSTA® should be used with caution when taking medications that may change the electrical activity of the heart (QT prolongation), such as but not restricted to: medicines for malaria, heart rhythm disorders, allergies, other antipsychotics, antidepressants, water tablets or other medicines affecting body salts (sodium, potassium, magnesium).

- Carbamazepine and topiramate (drugs used to treat seizures), as these may change the effect of RISPERDAL CONSTA®.

- PROZAC® (fluoxetine), PAXIL® (paroxetine) (antidepressants) and CLOZARIL® (clozapine) (antipsychotic), as these may increase the level of RISPERDAL CONSTA® in your blood.

- LASIX® (furosemide): Studies in elderly patients with dementia have shown that taking RISPERDAL® along with furosemide, a medicine which is sometimes used to treat high blood pressure, some heart problems, or to treat swelling of parts of the body caused by the build-up of too much fluid, is associated with an increased rate of death (see **WARNINGS AND PRECAUTIONS**).

- Itraconazole and ketoconazole, medicines for treating fungal infections.

- Certain medicines used in the treatment of HIV/AIDS, such as NORVIR® (ritonavir).

- Verapamil, a medicine used to treat high blood

pressure and/or abnormal heart rhythm.

- Sertraline and fluvoxamine, medicines used to treat depression and other psychiatric disorders.

- Rifampicin, a medicine for treating some infections

PROPER USE OF THIS MEDICATION

Usual dose:
The usual dose is 25 mg given every two weeks by intramuscular injection either in the buttock or arm by your doctor. For some patients, a lower dose of 12.5 mg might be used. Injections should be alternated between right and left sides and should not be given intravenously. If you have never taken any form of RISPERDAL®, your physician may give you oral RISPERDAL®/RISPERDAL M-TAB® before beginning treatment with RISPERDAL CONSTA®.

Overdose:

If you have been given too much RISPERDAL CONSTA®, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

In overdose, one or more of the following signs may occur:
- reduced consciousness
- sleepiness
- excessive trembling
- excessive muscle stiffness
- fast beating heart
- dizziness or
  light-headedness when standing up

Missed dose:
If you miss an appointment, you should contact your doctor right away to let him or her know you missed your injection. Your doctor will then advise you when to come next for your scheduled appointment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

These are not all the possible side effects you may feel when taking RISPERDAL CONSTA®. If you experience any side effects not listed here, contact your healthcare professional.

Side effects that may occur very commonly are common cold symptoms, difficulty falling or staying asleep, depression, anxiety, trembling, decreased motor function or activity such as slight muscle stiffness, increased saliva and/or drooling, and headache.

Side effects that may occur commonly include: pneumonia, urinary tract infection, feeling like you have the flu, anemia, sleep disorder, irritability, weight loss, uncontrollable movements of the face or body, rigid muscles, slowness of movement and muscle stiffness or spasm, tremor, blurry vision, faster heart rate, low blood pressure, high blood pressure, abdominal pain, nausea/vomiting, constipation, diarrhea, indigestion, dry mouth, muscle spasms, loss of urine, swelling of the body, arms or legs, weakness, fatigue, increased liver transaminases in your blood, and a reaction at the injection site including itching, pain or swelling.

RISPERDAL CONSTA®can raise your levels of a hormone called “prolactin:. This is measured with a blood test. Symptoms may include:
- In men:
  - swelling in the breast
  - difficulty in getting or maintaining an erection or other sexual dysfunction.
- In women
  - discomfort in the breasts
  - leaking of milk from the breasts (even if not pregnant)
  - missing your menstrual period or other problems with your cycle

If you have high levels of prolactin and a condition called hypogonadism you may be at an increased risk of breaking a bone due to osteroporosis. This occurs in both men and women.

High blood sugar has been reported. See your doctor if you experience symptoms, such as excessive thirst or urination.

Uncommon side effects may include: sugar in the urine, diabetes mellitus or worsening of diabetes, high blood triglycerides (a fat), increased cholesterol in your blood, mania, a restless urge to move parts of your body, concentration difficulties, nervousness, itching, joint swelling, swelling of the ankles, heartbeat irregularities and changes in body temperature .

RISPERDAL CONSTA® may cause sudden dizziness or lightheadedness (symptoms of postural hypotension). You/the patient you are caring for should not rise rapidly after having been sitting or lying for prolonged periods, especially when you start taking RISPERDAL CONSTA®.

In rare cases, the following may happen: low blood sugar, and irregular heartbeat.

Lack of bowel muscle movement that causes blockage may occur very rarely.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM			
Symptom/effect	Call your doctor or pharmacist		Stop taking drug and seek immediate medical emergency help
	Only if severe	In all cases	
Common			
Skin rash on its own		✓	
Dystonia: twisting movements that you cannot control, and can affect posture or the face, including eyes, mouth, tongue or jaw		✓	
Uncommon			
Seizure (i.e., loss of consciousness with uncontrollable shaking)			✓
Tardive Dyskinesia: Muscle twitching or abnormal movements of the face or tongue or body		✓	
Severe allergic reaction: fever, itching, skin rash, swelling of the mouth, face, lips or tongue, shortness of breath, and sometimes a drop in blood pressure (amounting to an "anaphylactic reaction")			✓
Dysphagia: Difficulty swallowing that can cause food or liquids to get into your lungs		✓	
Rare			
Inflammation of the pancreas: severe abdominal pain, fever, nausea, vomiting			✓
Jaundice: yellowing of the skin and eyes, dark urine			✓
Rhabdomyolysis: Very dark ("tea coloured") urine, muscle tenderness and/or aching			✓
Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.		✓	
A state of confusion, reduced consciousness, high fever, or pronounced muscle stiffness			✓
Decreased White Blood Cells: infections, fatigue, aches, pains and flu-like symptoms			✓
Very Rare			
Life-threatening complications of uncontrolled diabetes such as shortness of breath, confusion and loss of consciousness			✓
Marked changes in body temperature (generally as a result of several factors together including extreme heat or cold).			✓
Sudden loss of vision or blindness			✓
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
Sudden change in mental state or sudden weakness or numbness of the face, arms or legs, especially on one side, slurred speech or vision problems, even for a short period of time			✓
Bruise easily, excessive bleeding		✓	

Injection site reactions that may require medical attention, including accumulation of pus caused by bacterial infection, deep skin infection, a sac or lump under the skin, accumulation of blood or severe bruise, dead cells or tissues, and skin ulcer		✓	
Symptoms of muscle breaking down such as pain, weakness and swelling of the muscles – can be detected by blood test/can lead to kidney failure			✓
Serious Allergic reactions even if you have previously tolerated oral risperidone or oral paliperidone; symptoms include rash, swelling of your throat, itching or problems breathing. These may be signs of a serious allergic reaction.			✓

If you have a troublesome symptoms or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Store RISPERDAL CONSTA® in its original package in the refrigerator at 2°C–8°C, protected from light. If refrigeration is not available, store at temperatures not exceeding 25°C and protected from light for no more than 7 days. Do not expose unrefrigerated product to temperatures above 25°C.
Keep RISPERDAL CONSTA® out of the reach of children.

The expiry date for RISPERDAL CONSTA® is printed on the package. Do not use the medicine in the package after this date.

MORE INFORMATION

For questions, concerns, or the Product Monograph go to www.janssen.com/canada
or contact the manufacturer, Janssen Inc., at:
1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by
Janssen Inc.
Toronto, Ontario M3C 1L9

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