PRODUCT NAME
RISPERDAL®

DOSAGE FORM AND STRENGTHS
Tablets:
Film-coated tablets for oral use:
- 1 mg risperidone as white half-scored oblong biconvex tablets;
- 2 mg risperidone as orange half-scored oblong biconvex tablets;

Oral Solution:
Oral solution 1 mg/ml risperidone.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION
Indications
RISPERDAL® is indicated for the treatment of a broad range of patients with schizophrenia, including first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. RISPERDAL® alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. RISPERDAL® is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

RISPERDAL® is indicated for the short-term treatment of persistent aggression in patients with moderate to severe dementia of the Alzheimer's type unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.

RISPERDAL® is indicated for the treatment of behavioural disorders associated with autism (e.g. irritability, social withdrawal, stereotypic behaviour, hyperactivity and inappropriate speech) in children and adolescents.

RISPERDAL® is also indicated for bipolar mania.

Adjunctive therapy: RISPERDAL® is indicated as adjunctive therapy to mood stabilizers in the treatment of manic episodes associated with bipolar disorders. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviors.

Monotherapy: RISPERDAL® is indicated in the treatment of acute manic episodes associated with bipolar 1 disorder. The effectiveness of RISPERDAL® for more than 12 weeks of treatment of an acute episode, and for the prevention of new manic episodes has not been established. RISPERDAL® is indicated in the treatment of conduct and other disruptive behavior disorders in children (over 5 years), adolescents and adults with subaverage

intellectual functioning or mental retardation in whom destructive behaviors (e.g. aggression, impulsivity and self-injurious behaviors) are prominent.

As with all symptomatic treatments, the continued use of RISPERDAL® must be evaluated and justified on an ongoing basis.

Dosage and Administration

Dosage

Schizophrenia

Switching from other antipsychotics

When medically appropriate, gradual discontinuation of the previous treatment while RISPERDAL® therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medications should be re-evaluated periodically.

Adults

RISPERDAL® may be given once daily or twice daily.

Patients should start with 2 mg/day RISPERDAL®. The dosage may be increased on the second day to 4 mg. From then on the dosage can be maintained unchanged, or further individualized, if needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients, a slower titration phase and a lower starting and maintenance dose may be appropriate.

Doses above 10 mg/day have not been shown to be superior in efficacy to lower doses and may cause extrapyramidal symptoms. Since the safety of doses above 16 mg/day has not been evaluated, doses above this level should not be used.

A benzodiazepine may be added to RISPERDAL® when additional sedation is required.

Special populations

Elderly

A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily.

Children

Experience in schizophrenia is lacking in children less than 15 years of age.

Renal and liver disease

A starting dose of 0.5 mg twice daily is recommended. This dose can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily.

Bipolar mania

Adults

RISPERDAL® should be administered on a once daily schedule, starting with 2 or 3 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Efficacy was demonstrated in flexible doses over a range of

1 to 6mg per day. A dosing range between 2-6 mg per day is recommended. The physician who elects to use RISPERDAL® for periods extending beyond 12 weeks should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

As with all symptomatic treatments, the continued use or RISPERDAL® must be evaluated and justified on an ongoing basis.

Children
Experience is lacking in bipolar mania in children and adolescents less than 18 years of age.

Aggression in patients with Dementia of the Alzheimer type
A starting dose of 0.25 mg b.i.d. is recommended. This dosage can be individually adjusted by increments of 0.25 mg b.i.d., not more frequently than every other day, if needed. The optimum dose is 0.5 mg b.i.d. for most patients. Some patients, however, may benefit from doses up to 1 mg b.i.d.

There is no data to support treatment beyond 12 weeks in patients with moderate to severe dementia of the Alzheimer type with agitation, aggression or psychotic symptoms.

Once patients have reached their target dose, a once daily dosing regimen can be considered. As with all symptomatic treatments, the continued use or RISPERDAL® must be evaluated and justified on an ongoing basis.

Conduct and other disruptive behavior disorders (5-18 years of age)
For patients ≥ 50 kg, a starting dose of 0.5 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5 mg once daily not more frequently than every other day, if needed. The optimum dose is 1 mg once daily for most patients. Some patients, however, may benefit from 0.5 mg once daily while others may require 1.5 mg once daily.

For patients < 50 kg, a starting dose of 0.25 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5 mg once daily for most patients. Some patients, however, may benefit from 0.25 mg once daily while others may require 0.75 mg once daily.

As with all symptomatic treatments, the continued use of RISPERDAL® must be evaluated and justified on an ongoing basis.

Experience is lacking in children less than 5 years of age.

Autism
Pediatrics (5-17 years of age)
The dosage of RISPERDAL® should be individualized according to the needs and response of the patient.

Dosing should be initiated at 0.25 mg per day for patients <20 kg and 0.5 mg per day for patients ≥20 kg.

On Day 4, the dose may be increased by 0.25 mg for patients <20 kg and 0.5 mg for patients ≥20 kg.

This dose should be maintained and response should be assessed at approximately Day 14. Only in patients not achieving sufficient clinical response should additional dose increases be considered. Dose increases may proceed at ≥2-week intervals in increments of 0.25 mg for patients <20 kg or 0.5 mg for patients ≥20 kg.

In clinical studies, the maximum dose studied did not exceed a total daily dose of 1.5 mg in patients <20 kg, 2.5 mg in patients ≥20 kg, or 3.5 mg in patients >45 kg. Doses below 0.25mg/day were not effective in clinical studies.

Doses of RISPERDAL® in Pediatric Patients With Autistic Disorder
(**by total mg/day**)

Weight Categories	Days 1-3	Days 4 – 14+	Increments if Dose Increases are Needed	Dose Range
<20 kg	0.25 mg	0.5 mg	+0.25 mg at ≥ 2 week intervals	0.5 mg- 1.5 mg
≥20 kg	0.5 mg	1.0 mg	+0.5 mg at ≥ 2 week intervals	1.0 mg – 2.5 mg*

*Subjects weighing > 45 kg may require higher doses; maximum dose studied was 3.5 mg/ day

For prescribers preferring to dose on a mg/kg/day basis the following guidance is provided.

Doses of RISPERDAL® in Pediatric Patients With Autistic Disorder
(by mg/kg/day)

Weight Categories	Days 1-3	Days 4 – 14+	Increments if Dose Increases are Needed	Dose Range
All	0.01 mg/kg/day	0.02 mg/kg/day	+0.01 mg/kg/day at ≥ 2 week intervals	0.02 mg/kg/day – 0.06 mg/kg/day

RISPERDAL® can be administered once daily or twice daily

Patients experiencing somnolence may benefit from a switch in dosing from once daily to either once daily at bedtime or twice daily

Once sufficient clinical response has been achieved and maintained, consideration may be given to gradually lowering the dose to achieve the optimal balance of efficacy and safety.

Experience is lacking in children less than 5 years and limited in autistic adolescents.

Effectiveness for more than 8 weeks has not been systematically evaluated in double-blind, parallel-controlled clinical trials. Therefore, the physician who elects to use RISPERDAL® for the treatment of behavioral disorders associated with autism (e.g. irritability, social withdrawal, stereotypic behaviour, hyperactivity and inappropriated speech) in children and adolescents for extended periods should periodically re-evaluate the long term risks and benefits of the drug for the individual patient.

Renal and hepatic impairment
Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.

Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

RISPERDAL® should be used with caution in these groups of patients.

Administration
RISPERDAL® may be given as oral tablets or oral solution.

Contraindications
RISPERDAL® is contraindicated in patients with a known hypersensitivity to the product.

Warnings and Precautions
Elderly patients with dementia
Overall mortality
Elderly patients with dementia treated with atypical antipsychotic drugs have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including RISPERDAL®. In placebo-controlled trials with RISPERDAL® in this population, the incidence of mortality was 4.0% for RISPERDAL®-treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100).

Concomitant use with furosemide
In the RISPERDAL® placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.

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

Cerebrovascular adverse events (CAE)
For specific dosage recommendations for elderly patients, patients with renal and liver disease and patients with dementia, see *Dosage and Administration*. Cerebrovascular adverse events (e.g. stroke, transient ischemic attack), including fatalities, were reported in patients (mean age

85 years range; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis.

In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis.

In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with RISPERDAL® compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies in mainly elderly patients (>65 years of age) with dementia showed that CAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34, 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. RISPERDAL® should be used with caution in patients with risk factors for stroke.

The risk of CAEs was higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia.

Physicians are advised to assess the risks and benefits of the use of RISPERDAL® in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient. Patients/caregivers should be cautioned to immediately report signs and symptoms of potential CAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of risperidone.

Patients should be reassessed regularly, and the need for continuing treatment reassessed.

Orthostatic hypotension

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. RISPERDAL® should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see *Dosage and Administration*). A dose reduction should be considered if hypotension occurs.

Leucopenia, neutropenia, and agranulocytosis

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

Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of RISPERDAL® 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.

Venous thromboembolism

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

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. Because RISPERDAL® has a lower potential to induce extrapyramidal symptoms than classical neuroleptics, it should have a reduced risk of inducing tardive dyskinesia as compared to classical neuroleptics. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

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

Neuroleptic Malignant Syndrome (NMS)

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

Parkinson's Disease and Dementia with Lewy Bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including RISPERDAL®, 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.

Hyperglycemia and diabetes mellitus

Hyperglycemia, diabetes mellitus and exacerbation of pre-existing diabetes have been reported in patients treated with atypical antipsychotics, including RISPERDAL®. 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. Any patient treated with atypical antipsychotics, including RISPERDAL® should be monitored for symptoms of hyperglycemia and diabetes mellitus (see *Adverse Reactions*). However, epidemiological studies suggest an increased risk of diabetes and hyperglycaemia with atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus, risk factors for diabetes (e.g. obesity, family history of diabetes), or those who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness.

Weight gain
Significant weight gain has been reported. Monitoring weight gain is advisable when RISPERDAL® is being used.

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

Priapism
Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with RISPERDAL® during postmarketing surveillance (see *Adverse Reactions*).

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

Antiemetic effect
An antiemetic effect was observed in preclinical studies with risperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

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

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

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.

Other

See "*Dosage and Administration*" for specific dosage recommendations for elderly patients, for elderly patients with dementia, for patients with bipolar mania, for pediatric patients with conduct and other disruptive behavior disorders, and for patients with renal or hepatic impairment.

For conduct disorder effects on sexual maturation and gonadal function in children and adolescents have not been evaluated beyond 12 months in relation to long-term treatment. Safety data beyond 12 months is lacking in relation to the effect of long-term treatment.

Interactions

Pharmacodynamic-related interactions

Centrally-acting drugs and alcohol

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

Levodopa and dopamine agonists

RISPERDAL® may antagonize the effect of levodopa and other dopamine agonists.

Psychostimulants

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

Drugs with hypotensive effects

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

Drugs known to prolong the QT interval

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

Pharmacokinetic-related interactions

Food does not affect the absorption of RISPERDAL®

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

Strong CYP2D6 inhibitors

Co-administration of RISPERDAL® with a strong CYP2D6 inhibitor may increase the plasma concentrations of risperidone, but less so of the active antipsychotic fraction. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active antipsychotic fraction (e.g., paroxetine, see below). When concomitant paroxetine or another strong CYP2D6

inhibitor, especially at higher doses, is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®.

CYP3A4 and/or P-gp inhibitors
Coadministration of RISPERDAL® 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®.

CYP3A4 and/or P-gp inducers
Co-administration of RISPERDAL® 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®.

Highly protein-bound drugs
When RISPERDAL® is taken together with other 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.

Pediatric population
Interaction studies have only been performed in adults. The relevance of the results from these studies in pediatric patients is unknown.

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

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

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

Antiepileptics:
- Carbamazepine, a strong CYP3A4 inducer and P-gp inducer, has been shown to decrease the plasma levels of the active antipsychotic fraction of risperidone.
- Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

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

Antifungals:

- Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70%, at risperidone doses of 2 to 8mg/day.
- Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200mg/day increased the plasma concentrations of risperidone and decreased the plasma concentration of 9-hydroxy-risperidone.

Antipsychotics:

- Phenothiazines, may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.
- Aripiprazole, a CYP2D6 and CYP3A4 substrate: There is insufficient clinical evidence to evaluate the effect of risperidone, on the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.

Antivirals:

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

Beta-Blockers:

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

Calcium Channel Blockers:

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

Digitalis Glycosides:

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

Diuretics:

- Furosemide: See section on *Warnings and Precautions* regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Gastrointestinal Drugs:

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

Lithium:

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

SSRIs and Tricyclic Antidepressants:

- Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone, but less so of the active antipsychotic fraction. Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20mg/day, less so of the active antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction.
- Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction.
- Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than 100mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.

Pregnancy and Breast-feeding

Pregnancy

The safety of risperidone for use during human pregnancy has not been established.

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

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

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

RISPERDAL® should only be used during pregnancy if the benefits outweigh the risks.

Breast-feeding

In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL® should not breast-feed.

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of risperidone based on the comprehensive assessment of the available adverse event information. A causal relationship with risperidone usually cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

The safety of RISPERDAL® was evaluated from a clinical trial database consisting of 9803 patients exposed to one or more doses of RISPERDAL® for the treatment of various psychiatric disorders in adults, elderly patients with dementia, and pediatrics. Of these 9803 patients, 2687 were patients who received RISPERDAL® while participating in double-blind, placebo-controlled trials. The conditions and duration of treatment with RISPERDAL® 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 3 years) exposures.

The majority of all adverse reactions were mild to moderate in severity.

Double-blind, placebo-controlled data – Adult patients

Adverse reactions reported by ≥ 1% of RISPERDAL®-treated adult patients in nine 3- to 8-week double-blind, placebo-controlled trials are shown in Table 1.

Table 1: Adverse Reactions Reported by ≥ 1% of RISPERDAL®-Treated Adult Patients in Double-Blind Placebo-Controlled Studies

System/Organ Class Adverse Reaction	**RISPERDAL® ≤8 mg/day (N=853) %**	**RISPERDAL® >8-16 mg/day (N=198) %**	**PLACEBO (N=687) %**
Infections and Infestations			
Nasopharyngitis	2.1	4.0	1.7
Upper respiratory tract infection	1.5	2.5	1.5
Sinusitis	0.7	1.5	0.6
Urinary tract infection	0.5	2.5	0.1
Blood and Lymphatic System Disorders			
Anemia	0.1	1.0	0.1
Immune System Disorders			
Hypersensitivity	0.1	1.0	0.1
Psychiatric Disorders			
Insomnia	16.2	25.3	13.2
Anxiety	7.7	11.1	4.4
Nervousness	0.5	1.0	0.1
Nervous System Disorders			

Parkinsonism*	19.3	17.2	7.9
Akathisia*	9.8	10.1	2.7
Somnolence	6.8	1.5	2.0
Dizziness	6.3	3.5	3.9
Sedation	4.6	3.0	1.3
Tremor*	4.2	2.5	2.5
Dystonia*	3.8	3.5	1.0
Lethargy	2.6	0	1.3
Dizziness postural	1.2	0	0.1
Dyskinesia*	1.2	2.0	0.9
Syncope	0.4	1.0	0
Eye Disorders			
Vision blurred	2.1	1.0	0.7
Ear and Labyrinth Disorders			
Ear pain	0.1	1.0	0.3
Cardiac Disorders			
Tachycardia	1.1	2.5	0.1
Vascular Disorders			
Orthostatic hypotension	1.3	0.5	0.1
Hypotension	0.2	1.0	0.3
Respiratory, Thoracic and Mediastinal Disorders			
Nasal congestion	2.0	6.1	1.3
Dyspnea	0.8	2.0	0
Epistaxis	0.5	1.5	0.1
Sinus congestion	0.5	1.0	0.6
Gastrointestinal Disorders			
Nausea	6.4	4.0	2.6
Constipation	4.6	9.1	3.6
Dyspepsia	4.3	6.1	2.6
Vomiting	3.9	4.5	3.8
Diarrhea	2.3	0.5	1.9
Salivary hypersecretion	2.3	1.0	0.4
Dry mouth	2.1	0	1.0
Abdominal discomfort	1.5	1.0	0.9
Abdominal pain	1.1	0.5	0.7
Stomach discomfort	1.1	1.0	0.6
Abdominal pain upper	0.7	1.0	0.1
Skin and Subcutaneous Tissue Disorders			
Rash	0.8	3.5	0.9
Dry skin	0.5	2.5	0.3
Dandruff	0.2	1.0	0
Seborrheic dermatitis	0.2	1.0	0
Hyperkeratosis	0	1.0	0.3
Musculoskeletal and Connective Tissue Disorders			
Back pain	2.5	1.0	1.6
Arthralgia	1.5	2.5	0.6
Pain in extremity	1.2	1.0	2.2
Renal and Urinary Disorders			
Urinary incontinence	0.2	1.0	0.3
Reproductive System and Breast Disorders			
Ejaculation failure	0.4	1.0	0
General Disorders			
Fatigue	2.3	1.0	1.0
Asthenia	1.3	0.5	0.6
Pyrexia	1.3	1.0	0.7
Chest pain	0.8	1.5	0.4
Investigations			

Blood creatine phosphokinase increased	0.4	1.5	0.1
Heart rate increased	0.2	1.5	0.1

* Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, Parkinsonism, cogwheel rigidity, akinesia, bradykinesia, hypokinesia, masked facies, muscle rigidity, and Parkinson's disease. Akathisia includes akathisia and restlessness. Dystonia includes dystonia, muscle spasms, muscle contractions involuntary, muscle contracture, oculogyration, tongue paralysis. Tremor includes tremor and Parkinsonian rest tremor. Dyskinesia includes dyskinesia, muscle twitching, chorea, and choreoathetosis.

Double-blind, Placebo-controlled data – Elderly patients with dementia

Adverse reactions reported by ≥ 1% of RISPERDAL®-treated elderly patients with dementia in six 4- to 12-week double-blind, placebo-controlled trials are shown in Table 2. Table 2 includes only those adverse reactions that are either not listed in Table 1 or those adverse reactions that occurred at ≥ 2 times the frequency of the adverse reactions listed in Table 1.

Table 2: Adverse Reactions Reported by ≥ 1% of RISPERDAL®-Treated Elderly Patients with Dementia in Double-Blind Placebo-Controlled Studies: Adverse Reactions Not Listed in Table 1 or Reported at ≥ 2 Times the Frequency of Adverse Reactions Listed in Table 1.

System/Organ Class Adverse Reaction	**RISPERDAL®** **(N=1009)** **%**	**PLACEBO** **(N=712)** **%**
Infections and Infestations		
Urinary tract infection	12.9	10.3
Pneumonia	3.1	2.4
Cellulitis	1.1	1.3
Metabolism and Nutrition Disorders		
Decreased appetite	2.3	1.4
Psychiatric Disorders		
Confusional state	2.7	0.1
Nervous System Disorders		
Lethargy	7.6	2.2
Transient ischemic attack	1.6	0.6
Depressed level of consciousness	1.3	0.3
Drooling	1.3	0
Cerebrovascular accident	1.1	0.4
Eye Disorders		
Conjunctivitis	2.7	1.1
Vascular Disorders		
Hypotension	2.2	1.4
Respiratory, Thoracic and Mediastinal Disorders		
Cough	4.6	3.1
Rhinorrhea	1.5	0.8
Gastrointestinal Disorders		
Dysphagia	1.5	1.3
Fecaloma	1.1	0.4
Skin and Subcutaneous Tissue Disorders		
Erythema	4.0	4.6
Musculoskeletal and Connective Tissue Disorders		
Posture abnormal	1.8	0.8
Joint swelling	1.5	0.3
General Disorders		
Edema peripheral	7.7	3.9
Pyrexia	4.0	1.8
Gait disturbance	3.5	1.5
Pitting edema	1.5	0.3
Investigations		
Body temperature increased	2.6	0.8

Double-blind, placebo-controlled data – Pediatric patients

Adverse reactions reported by ≥ 1% of RISPERDAL®-treated pediatric patients in eight 3- to 8-week double-blind, placebo-controlled trials are shown in Table 3. Table 3 includes only those adverse reactions that are either not listed in Table 1 or those adverse reactions that occurred at ≥ 2 times the frequency of the adverse reactions listed in Table 1.

Table 3: Adverse Reactions Reported by ≥ 1% of RISPERDAL®-Treated Pediatric Patients in Double-Blind Placebo-Controlled Studies: Adverse Reactions Not Listed in Table 1 or Reported at ≥ 2 Times the Frequency of Adverse Reactions Listed in Table 1.

System/Organ Class Adverse Reaction	RISPERDAL® ≤3 mg/day (N=344) %	RISPERDAL® >3-6 mg/day (N=95) %	PLACEBO (N=349) %
Infections and Infestations			
Upper respiratory tract infection	5.2	2.1	3.4
Rhinitis	3.5	1.1	3.2
Influenza	1.7	0	1.7
Metabolism and Nutrition Disorders			
Increased appetite	17.2	3.2	7.2
Psychiatric Disorders			
Middle insomnia	1.7	0	0.9
Listless	0.9	1.1	0
Nervous System Disorders			
Somnolence	26.5	15.8	7.7
Headache	22.4	21.1	14.9
Sedation	20.1	14.7	4.0
Dizziness	8.1	13.7	2.3
Tremor	6.1	8.4	1.1
Drooling	4.9	2.1	1.1
Dysarthria	1.5	1.1	0
Disturbance in attention	0.9	1.1	0.6
Balance disorder	0.9	1.1	0
Hypersomnia	0.6	1.1	0.9
Cardiac Disorders			
Palpitations	0.6	2.1	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	8.7	3.2	6.6
Rhinorrhea	4.9	2.1	3.4
Epistaxis	3.8	4.2	1.7
Pharyngolaryngeal pain	3.8	2.1	1.7
Pulmonary congestion	0.3	1.1	0.3
Gastrointestinal Disorders			
Vomiting	13.7	8.4	9.2
Abdominal pain upper	8.4	6.3	4.6
Diarrhea	6.7	2.1	6.0
Salivary hypersecretion	3.5	6.3	0.9
Stomach discomfort	2.9	0	1.4
Abdominal pain	2.3	2.1	0.6
Skin and Subcutaneous Tissue Disorders			
Pruritus	1.2	0	0
Acne	0.9	1.1	0
Musculoskeletal and Connective Tissue Disorders			
Myalgia	1.2	1.1	0.9
Neck pain	0.3	1.1	0.3
Renal and Urinary Disorders			
Enuresis	6.4	1.1	5.2
Urinary incontinence	2.0	0	1.4
Pollakiuria	1.5	1.1	0.3
Reproductive System and Breast Disorders			
Galactorrhea	0.6	2.1	0
General Disorders			
Fatigue	19.2	18.9	4.9
Pyrexia	8.4	3.2	6.3

Feeling abnormal	1.2	0	0
Sluggishness	0.9	1.1	0
Chest discomfort	0.3	1.1	0
Investigations			
Weight increased	4.9	2.1	0.9
Blood prolactin increased	3.8	0	0.3

Other clinical trial data

Paliperidone is the active metabolite of risperidone, therefore the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. Hence, a comprehensive listing of adverse reactions across paliperidone and risperidone products provides relevant safety information for these related products. Adverse reactions detected for one formulation of risperidone or paliperidone were considered as relevant safety information for the other formulation of the same compound unless the adverse reaction was unique to either the formulation or the route of administration. Adverse reactions for one compound that were not listed for the other compound were also added to the label for the other compound unless no meaningful new safety information could be derived from the additional adverse reactions (i.e. the term was vague or the medical concept was already found in the current label). All adverse reactions and their frequencies of occurrence in patients on RISPERDAL® are reflected in the Adverse Reactions tables below.

Table 4: **Additional Adverse Reactions Reported with Risperidone and/or Paliperidone by ≥1% of RISPERDAL®-treated Subjects[1] (The Terms within each System Organ Class are Sorted Alphabetically)**

System/Organ Class Adverse Reaction
Psychiatric disorders Agitation, Insomnia*
Nervous system disorders Akathisia*, Dyskinesia*, Dystonia*, Parkinsonism*
Vascular disorders Hypertension
Musculoskeletal and connective tissue disorders Musculoskeletal pain
General disorders and administration site conditions Gait abnormal, Edema*, Pain
Injury, poisoning and procedural complications Fall

* **Insomnia includes:** initial insomnia, middle insomnia; **Akathisia includes:** hyperkinesia, restless legs syndrome, restlessness; **Dyskinesia includes:** athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus; **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; **Parkinsonism includes:** akinesia, bradykinesia, cogwheel rigidity, drooling, extrapyramidal symptoms, glabellar reflex abnormal, muscle rigidity, muscle tightness, musculoskeletal stiffness; **Edema includes:** generalized edema, edema peripheral, pitting edema.

[1]Frequencies calculated based on a pooled dataset of the 23 double-blind, placebo-controlled pivotal studies- 9 in adults, 6 in elderly patients with dementia, and 8 in pediatric patients

Adverse reactions reported with risperidone and/or paliperidone by < 1% of RISPERDAL®-treated subjects in a pooled dataset of 23 double-blind, placebo-controlled pivotal studies (9 in adults, 6 in elderly patients with dementia, and 8 in pediatric patients) are shown in Table 5.

Table 5: Additional Adverse Reactions Reported with Risperidone and/or Paliperidone by < 1% of RISPERDAL®-treated Subjects[1] (The Terms within each System Organ Class are Sorted Alphabetically).

System/Organ Class Adverse Reaction
Infections and infestations Acarodermatitis, Bronchitis, Cystitis, Ear infection, Eye infection, Infection, Localized infection, Onychomycosis, Respiratory tract infection, Tonsillitis, Viral infection
Blood and lymphatic system disorders Eosinophil count increased, Hematocrit decreased, Neutropenia, White blood cell count decreased
Endocrine disorders Glucose urine present, Hyperprolactinemia
Metabolism and nutrition disorders Anorexia, Blood cholesterol increased, Blood triglycerides increased, Hyperglycemia, Polydipsia, Weight decreased
Psychiatric disorders Blunted affect, Depression, Libido decreased, Nightmare, Sleep disorder
Nervous system disorders Cerebrovascular disorder, Convulsion*, Coordination abnormal, Diabetic coma, Hypoesthesia, Loss of consciousness, Paresthesia, Psychomotor hyperactivity, Tardive dyskinesia, Unresponsive to stimuli
Eye disorders Dry eye, Eye rolling, Eyelid margin crusting, Glaucoma, Lacrimation increased, Ocular hyperemia
Ear and labyrinth disorders Tinnitus, Vertigo
Cardiac disorders Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Sinus arrhythmia
Vascular disorders Flushing
Respiratory, thoracic and mediastinal disorders Dysphonia, Hyperventilation, Pneumonia aspiration, Rales, Respiratory disorder, Respiratory tract congestion, Wheezing
Gastrointestinal disorders Cheilitis, Fecal incontinence, Flatulence, Gastroenteritis, Swollen tongue, Toothache
Hepatobiliary disorders Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased
Skin and subcutaneous tissue disorders Eczema, Skin discoloration, Skin disorder, Skin lesion
Musculoskeletal and connective tissue disorders Joint stiffness, Muscular weakness, Rhabdomyolysis
Renal and urinary disorders Dysuria
Reproductive system and breast disorders Amenorrhea, Breast discharge, Ejaculation disorder, Erectile dysfunction, Gynecomastia, Menstrual disorder*, Sexual dysfunction, Vaginal discharge
General disorders and administration site conditions Body temperature decreased, Chills, Discomfort, Drug withdrawal syndrome, Face edema, Malaise, Peripheral coldness, Thirst
Injury, poisoning and procedural complications Procedural pain

***Convulsion includes:** Grand mal convulsion; **Menstrual disorder includes:** Menstruation irregular, Oligomenorrhea

[1]Frequencies calculated based on a pooled dataset of the 23 double-blind, placebo-controlled pivotal studies- 9 in adults, 6 in elderly patients with dementia, and 8 in pediatric patients.

Adverse reactions reported with risperidone and/or paliperidone in other clinical trials but not reported by RISPERDAL®-treated subjects in a pooled dataset of 23 double-blind, placebo-controlled pivotal studies are shown in Table 6.

Table 6: Additional Adverse Reactions Reported with Risperidone and/or Paliperidone in Other Clinical Trials but Not Reported by RISPERDAL®-treated Subjects in Trials Listed in Tables 4 and 5[1] (The Terms within each System Organ Class are Sorted Alphabetically)

System/Organ Class Adverse Reaction
Immune system disorders Anaphylactic reaction
Metabolism and nutrition disorders Hyperinsulinemia
Psychiatric disorders Anorgasmia
Nervous system disorders Head titubation, Neuroleptic malignant syndrome
Eye disorders Eye movement disorder, Photophobia
Cardiac disorders Postural orthostatic tachycardia syndrome
Gastrointestinal disorders Intestinal obstruction
Skin and subcutaneous tissue disorders Drug eruption, Urticaria
Reproductive system and breast disorders Breast discomfort, Breast engorgement, Breast enlargement, Menstruation delayed
General disorders and administration site conditions Induration

[1]Frequencies of adverse reactions listed in Tables 4 and 5 were calculated from the 23 double-blind, placebo-controlled pivotal studies- 9 in adults, 6 in elderly patients with dementia, and 8 in pediatric patients. The adverse reactions listed in the table above were not observed in these studies, but were observed in other, nonpivotal clinical studies with RISPERDAL® or in clinical studies with another risperidone- or paliperidone-containing product.

Postmarketing Data

Adverse events first identified as adverse reactions during postmarketing experience with risperidone and/or paliperidone are included in Table 7. In the table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports
Unknown	Cannot be estimated from the available data

In Table 7, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 7: Adverse Reactions Identified During Postmarketing Experience with Risperidone and/or Paliperidone. (The Frequency Is Based on Spontaneous Reporting Rates with Risperidone.)	
Blood and Lymphatic Disorders	
Very rare	Agranulocytosis, Thrombocytopenia
Endocrine Disorders	
Very rare	Inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders	
Very rare	Diabetes mellitus, Diabetic ketoacidosis, Hypoglycemia, Water intoxication
Psychiatric Disorders	
Very rare	Catatonia, Mania, Somnambulism, Sleep-related eating disorder
Nervous System Disorders	
Very rare	Dysgeusia
Eye Disorders	
Very rare	Floppy iris syndrome (intraoperative)
Cardiac Disorders	
Very rare	Atrial fibrillation
Vascular Disorders	
Very rare	Deep vein thrombosis, Pulmonary embolism
Respiratory, Thoracic, and Mediastinal Disorders	
Very rare	Sleep apnea syndrome
Gastrointestinal Disorders	
Very rare	Pancreatitis, Ileus
Hepatobiliary Disorders	
Very rare	Jaundice
Skin and Subcutaneous Tissue Disorders	
Very rare	Alopecia, Angioedema, Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and Urinary Disorders	
Very rare	Urinary retention
Pregnancy, Puerperium and Perinatal Conditions	
Very rare	Drug withdrawal syndrome neonatal
Reproductive System and Breast Disorders	
Very rare	Priapism
General Disorders	
Very rare	Hypothermia

Overdose

Symptoms and signs

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsade de pointes has been reported in association with combined overdose of oral RISPERDAL® and paroxetine.

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

Treatment

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to

detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08

Mechanism of action

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to $alpha_1$-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. 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 than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Pharmacokinetic Properties

RISPERDAL® oral solution is bio-equivalent to RISPERDAL® oral tablets.

Absorption

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absorption is not affected by food and thus risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and $alpha_1$-acid glycoprotein. The plasma protein binding of risperidone is 88%, that of 9-hydroxy-risperidone is 77%.

One week after administration, 70% of the dose is excreted in the urine and 14% in the feces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the dose. The remainder is inactive metabolites.

Metabolism

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

Elimination
After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active antipsychotic fraction is 24 hours.

Dose proportionality
Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4-5 days of dosing. Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

Special populations
Pediatrics
The pharmacokinetics of risperidone, 9-hydroxy-risperidone and the active antipsychotic fraction in children are similar to those in adults.

Renal and hepatic impairment
A single-dose study showed higher active plasma concentrations and a reduced clearance of the active antipsychotic fraction by 30% in the elderly and 60% in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35%.

NON-CLINICAL INFORMATION
In (sub)chronic toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependent effects were present in male and female genital tract and mammary gland.
These effects were related to the increased serum prolactin levels, resulting from the dopamine D2-receptor blocking activity of risperidone. In a toxicity study with juvenile rats, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs, sexual maturation was delayed. Long bone growth was not affected at a dose similar to the maximum human dose in adolescents (6 mg/day); effects were observed at a dose 4-fold (on an AUC basis) or 7-fold (on a mg/m^2 basis) the maximum human dose in adolescents.

All other safety data relevant to the prescriber have been included in the appropriate section.

PHARMACEUTICAL INFORMATION
List of Excipients
Film-coated tablets:
Tablet core
Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hypromellose 2910 15 mPa.s
Magnesium stearate
Colloidal anhydrous silica

Sodium lauryl sulfate

Film-coating
Hypromellose 2910 5 mPa.s
Propylene glycol
Titanium dioxide [(a)]
Talc[(a)]
Orange yellow S aluminum lake [(a)]

Oral solution:
Tartaric acid
Benzoic acid
Sodium hydroxide
Purified water

[(a)]Only in 2 mg oral tablets.

Incompatibilities
RISPERDAL® tablets: none.
RISPERDAL® oral solution: incompatible with tea.

Shelf Life
Refer to expiry date on the Outer Carton

RISPERDAL® Oral Solution:
Opened container – 3 months for all climatic zones when protected from freezing.

Storage Conditions
RISPERDAL® oral tablets should be stored between 15°C and 30°C.
RISPERDAL® oral solution should be stored between 15°C and 30°C and should be protected from freezing.

Keep out of reach of children.

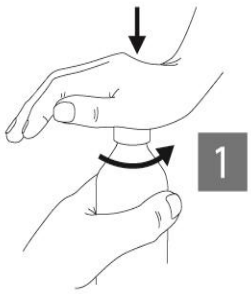
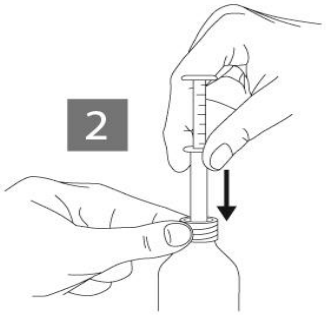
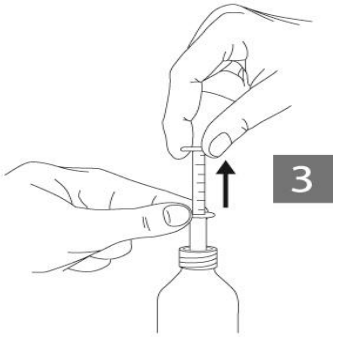
Nature and Contents of Container
Oral tablets:
PVC-PE-PVDC/Al blister consisting of aluminum foil 20 Tm with a 6 g/m² heat-seal coating and a trilayer foil PVC 200 Tm, LDPE 25 Tm, PVCD 90 g/m².

RISPERDAL® 1 and 2 mg tablets are individually packaged in a blister card containing 10 tablets. Blisters are packed in a cardboard box (2 or 6 blisters per box).

Oral solution:
RISPERDAL® Oral Solution is provided in 30 ml and 100 ml amber glass bottles with plastic child resistant closures.

The pipette supplied with the 30 ml and 100 ml bottle is calibrated in milligrams and milliliters with a minimum volume of 0.25 ml and a maximum volume of 3 ml. Calibration marks every 0.25 ml up to 3 ml are printed on this pipette.

Instructions for Use/Handling

Oral Solution Fig. 1: The bottle comes with a child-resistant cap, and should be opened as follows: – Push the plastic screw cap down while turning it counter clockwise. – Remove the unscrewed cap.	Dispensing Diagram 
Fig. 2: Insert the pipette into the bottle.	
Fig 3: While holding the bottom ring, pull the top ring up to the mark that corresponds to the number of milliliters or milligrams you need to give.	
Fig. 4: Holding the bottom ring, remove the entire pipette from the bottle. Empty the pipette into any non-alcoholic drink, except for tea, by sliding the upper ring down. Close the bottle. Rinse the pipette with some water.	

PRODUCT REGISTRANT

Johnson & Johnson International (Singapore) Pte. Ltd.
2 Science Park Drive

#07-13, Ascent
Singapore Science Park 1
Singapore 118222

BATCH RELEASER

Oral tablets:

Janssen-Cilag S.p.A.
Via C. Janssen, Borgo S. Michele
04100 Latina, Italy

Oral solution:

Janssen Pharmaceutica N.V.
Turnhoutseweg 30
B-2340 Beerse
Belgium

LAST DATE OF REVISION OF THE TEXT

15 September 2022 (CCDS 07 April 2020)