เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

1. PRODUCT NAME

RISPERDAL® ORAL SOLUTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Risperidone

2.2 Quantitative Declaration

The oral solution contains 1 mg/ml risperidone.

For excipients, see *section 6.1 List of Excipients*.

3. PHARMACEUTICAL FORM

Oral Solution.
The solution is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

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 adult patients who have shown an initial treatment response.

RISPERDAL is indicated for 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.

RISPERDAL is indicated for the treatment (up to 12 weeks) of agitation, aggression or psychotic symptoms in patients with moderate to severe dementia of the Alzheimer type.

RISPERDAL is indicated in the treatment of conduct and other disruptive behavior disorders where aggressive or other disruptive behaviors are prominent. RISPERDAL is also effective in maintaining the clinical improvement during continuation therapy in children and adolescents who have shown an initial treatment response.

RISPERDAL is indicated for the treatment of autism in children and adolescents.

4.2 Posology and method of 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

Pediatrics (13-17 years of age)

A starting dose of 0.5 mg daily is recommended, administered as a single-daily dose either in the morning or evening. If indicated, this dosage can then be adjusted at intervals not less than 24 hours in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 3 mg/day. Efficacy has been demonstrated at doses between 1 and 6 mg/day. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Experience in schizophrenia is lacking in children less than 13 years of age.

Elderly (65 years of age and older)

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.

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 6 mg per day.

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

Special populations

Pediatrics (10-17 years of age)

A starting dose of 0.5 mg once daily is recommended, administered as a single-daily dose in either the morning or evening. If indicated, this dosage can then be adjusted at intervals not less than 24 hours in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 2.5 mg/day. Efficacy has been demonstrated at doses between 0.5 and 6 mg/day. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

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

Experience is lacking in bipolar mania in children less than 10 years of age.

Agitation, aggression or psychotic symptoms in patients with dementia of the Alzheimer type

A starting dose of 0.25 mg twice daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg twice daily, not more frequently than every other day, if needed. The optimum dose is 0.5 mg twice daily for most patients. Some patients, however, may benefit from doses up to 1 mg twice daily.

Once patients have reached their target dose, a once daily dosing regimen can be considered. As with all symptomatic treatments, the continued use of 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 subjects < 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 0.25 mg/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

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 of age.

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.

4.3 Contraindication

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

4.4 Special warning and precautions for use

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)

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

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 *section 4.2 Posology and method of 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 (< 1/10000 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 $<1\times 10^9$/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 *section 4.5 Interaction with other medicinal products and other forms of 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 during treatment with 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 *section 4.8 Undesirable effects*).

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 *section 4.8 Undesirable effects*).

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 *section 4.8 Undesirable effects*).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Other

See *section 4.2 Posology and method of administration – Schizophrenia - Elderly* for specific posology recommendations for elderly patients, section *4.2 Posology and method of administration - Agitation, aggression or psychotic symptoms in patients with dementia of the Alzheimer type* for elderly patients with dementia of the Alzheimer type, section *4.2 Posology and method of administration - Bipolar mania* for patients with bipolar mania, *4.2 Posology and method of administration – Conduct and other disruptive behavior disorders* for pediatric patients with conduct and other disruptive behavior disorders, *4.2 Posology and method of administration-Autism* for pediatric patients with autism, and *4.2 Posology and method of administration – Renal and Hepatic Impairment* for patients with renal or hepatic impairment.

4.5 Interaction with other medicinal products and other forms of 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 *section 4.4 Special warning and precautions for use*).

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

Anticholinesterases:

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

Antiepileptics:

- Carbamazepine, a strong CYP3A4 inducer and a 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.
- Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antifungals:

- Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70%, at risperidone doses of 2 to 8 mg/day.
- Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of risperidone and decreased the plasma concentrations of 9-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: Risperidone tablets or injections did not affect the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.

Antivirals:

- Protease inhibitors: No formal study data are available; however, since ritonavir is a strong CYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of 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 *4.4 Special warning and precautions for use* 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 20 mg/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 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.

4.6 Pregnancy and lactation

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.

4.7 Effects on Ability to Drive and Use Machine

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.

4.8 Undesirable effects

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 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. This subsection includes additional adverse reactions reported with risperidone and/or paliperidone in clinical trials. 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 4.

Table 4: Adverse Reactions Reported with Risperidone and/or Paliperidone by ≥1% of RISPERDAL-treated Subjects in 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 (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.

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: 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. (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

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

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: 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. (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

Postmarketing data

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

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 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 by Frequency Category Estimated from 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

4.9 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. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08.

Mechanism of action

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-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.

5.2 Pharmacokinetic Properties

RISPERDAL oral solution is bioequivalent 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 represents 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

Steadystate 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%.

5.3 PRECLINICAL SAFETY DATA

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 D_2-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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Oral solution:

Tartaric acid

Benzoic acid

Sodium hydroxide

Purified water

6.2 Incompatibilities

RISPERDAL oral solution: incompatible with tea.

6.3 Shelf Life

See expiry date on the outer pack.

oral solution:

- Opened container – 3 months for all climatic zones when protected from freezing.

6.4 Special precautions for storage

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

Keep out of sight and reach of children.

6.5 Nature and Contents of Container

Oral solution

Colourless, clear solution

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

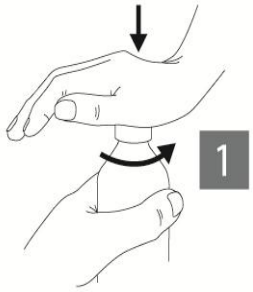
The pipette supplied with the 30 ml and 100 ml bottle is calibrated in milligrams and milliliters with a minimum volume of 0.25 ml and a maximum volume of 3 ml. Calibration marks every 0.25 ml up to 3 ml are printed on this pipette.

Instructions for Use and Handling

Always take this medicine exactly as your healthcare provider has told you. Check with your healthcare provider if you are not sure.

The solution comes with a syringe (pipette). Use only the syringe (pipette) delivered with this medicine for measuring the dose prescribed by your physician.

<table>
<tr><td>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.</td><td>Dispensing Diagram
 

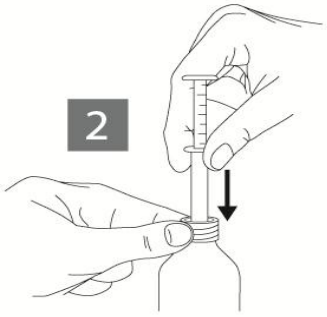
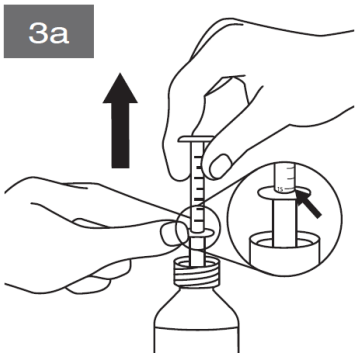
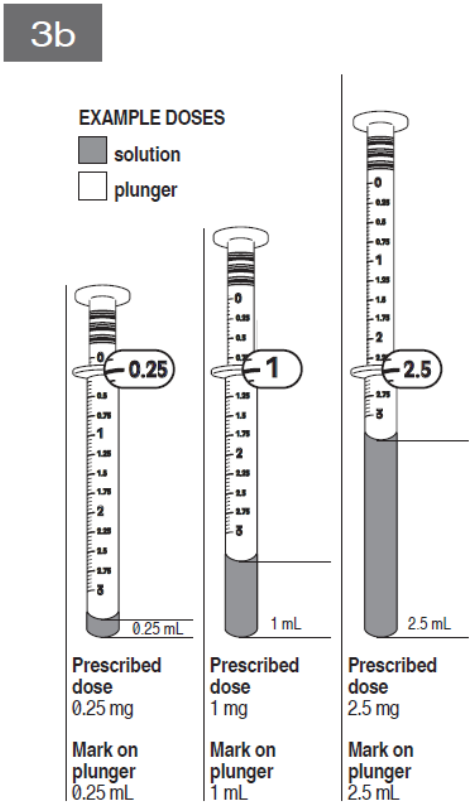
-</td></tr>
<tr><td>Fig. 2: Insert the pipette into the bottle.</td><td> 
</td></tr>
</table>

Fig. 3: While holding the bottom ring (Fig. 3a), pull the top ring up to the mark that corresponds to the number of milliliters or milligrams you need to give (See examples Fig. 3b).	
Measure the exact dose of medicine you need. Pay attention when measuring a small dose. For example, for 0.25 mg, measure 0.25 ml (a quarter milliliter); for 0.5 mg, measure 0.5 ml (half a milliliter). 1 ml of RISPERDAL oral solution contains 1 mg risperidone. The measured volume is printed every 0.25 ml / 0.25 mg on the plunger. Fig. 3b shows **examples** of prescribed doses and corresponding marks on the plunger.	
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 and let it air dry.	

7. MARKETING AUTHORIZATION HOLDER

See the end of leaflet

8. Marketing Authorization Number

1C 142/42(N)

9. Date of Authorization

Initial Authorization Date: 10 November 1999

10. DATE OF REVISION OF THE TEXT

CCDS version 04-Sep-2025

Manufactured by

Janssen Pharmaceutica N.V., Beerse, Belgium

Imported by

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To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com

For any product information, please contact us at medinfosea@its.jnj.com