Public Assessment Report

Decentralised Procedure

Risperidone 1mg/ml Oral Solution

Risperidone

UK/H/1174/01/DC

UK licence no: PL 29831/0349

Applicant: Wockhardt UK Limited

LAY SUMMARY

The MHRA granted Wockhardt UK Limited Marketing Authorisation (licence) for the medicinal product Risperidone 1mg/ml oral solution (PL 29831/0349) on 21st August 2008. This is a prescription-only medicine (POM).

This is a Decentralised application for Risperidone 1mg/ml oral solution submitted under Article 10.1 of Directive 2001/83. A pilot bioequivalence study was carried out to compare Wockhardt's Risperidone 1mg/ml oral solution against EU reference product Risperdal Liquid, these were found to be bioequivalent.

Risperidone is one of a group of medicines called antipsychotics which are used to treat certain types of mental illnesses that can affect the way you think, feel, speak and behave The symptoms of these illnesses include delusions, hallucinations, unusual suspiciousness and becoming withdrawn. People suffering from these illnesses may also feel depressed, tense or anxious.

Risperidone is also used to treat the symptoms of bipolar disorder which include feeling "high" or excited, having excessive amounts of energy, needing less sleep than usual and being more talkative with racing thoughts.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Risperidone 1mg/ml oral solution outweigh the risks, hence Marketing Authorisation has been granted.

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Module 1

Product Name	Risperidone 1mg/ml Oral Solution
Type of Application	Generic, Article 10.1
Active Substance	Risperidone
Form	1mg/ml Oral Solution
Strength	1mg/ml
MA Holder	Wockhardt UK Limited
RMS	UK
CMS	IE
Procedure Number	UK/H/1174/01/DC
Timetable	Day 150– 30th July 2008

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Risperidone 1mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution contains 1mg of risperidone.
Excipients: sodium methylparaben (E219) 1.8mg/ml.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Oral solution
The solution is clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, 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. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone is indicated for the treatment of mania in bipolar disorder. 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 behaviours.

Risperidone is not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 Posology and method of administration
1 ml of Risperidone Oral Solution contains 1 mg risperidone. If necessary Risperidone Oral Solution may be diluted with mineral water, orange juice or black coffee. When diluted in this way, the product should be used immediately. The liquid should not be mixed with tea.
(See Section 6. Pharmaceutical Particulars).

a Schizophrenia:
Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while risperidone therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating risperidone therapy in place of the next scheduled injection. The need for continuing existing antiparkinson medication should be re-evaluated periodically.

Adults
Risperidone Oral Solution may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day risperidone. The dosage may be increased to 4 mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.

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

Children
Use of risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

Renal and liver disease
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperidone should be used with caution in this group of patients until further experience is gained.

b Bipolar Mania:

Adults
Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.
As with all symptomatic treatments, the continued use of risperidone must be evaluated and justified on an ongoing basis.

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

Renal and liver disease
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.
Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers
There is limited information on the combined use of risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of risperidone producing lower plasma levels of the antipsychotic fraction of risperidone (see Section 4.5). It is therefore not recommended to co-administer risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of risperidone.

Method of administration
Oral use.

4.3 Contraindications
Risperidone Oral Solution is contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

4.4 Special warnings and precautions for use
Elderly patients with dementia

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

In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however, the mechanism for an interaction is unclear. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent

diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAE)

Risperidone Oral Solution is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks). Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomised clinical trials conducted in elderly >65 years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with risperidone, compared with placebo. Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33, 7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with risperidone (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, atrial fibrillation, etc.

Alpha-blocking activity

Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperidone should be used with caution in patients with known cardiovascular disease including those associated with prolongation of the QT interval and the dose should be gradually titrated. In clinical trials, risperidone was not associated with an increase in QTc intervals. As with other antipsychotics, caution is advised when prescribing with medications known to prolong the QT interval.

If further sedation is required, an additional drug (such as a benzodiazepine) should be administered rather than increasing the dose of risperidone.

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all antipsychotic drugs including risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency.

Caution should also be exercised when prescribing risperidone to patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

Hyperglycemia

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with risperidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Other

Classical neuroleptics are known to lower the seizure threshold. Caution is recommended when treating patients with epilepsy.

As with other antipsychotics, patients should be advised of the potential for weight gain.

Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Use of risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

Sodium methylparaben may cause delayed allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Possible interactions of risperidone with other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally acting drugs including alcohol.

Risperidone may antagonise the effect of levodopa and other dopamine-agonists.

Carbamazepine has been shown to decrease the plasma levels of the antipsychotic fraction of risperidone. A similar effect might be anticipated with other drugs which stimulate metabolising enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of risperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of risperidone should be re-evaluated and decreased if necessary.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.
When risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

See section 4.4 (Special warnings and special precautions for use) regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of risperidone from the stomach.

4.6 Pregnancy and lactation

Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats. No teratogenic effect of risperidone was noted in any study. The safety of risperidone for use during human pregnancy has not been established. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone

during the last trimester of pregnancy. Therefore, risperidone should only be used during pregnancy if the benefits outweigh the risks.

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

4.7 Effects on ability to drive and use machines

Risperidone 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

Risperidone is generally well tolerated and in many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of risperidone include:

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions.

Cerebrovascular accidents have been observed during treatment with risperidone (see Section 4.4 Special warnings and precautions for use).

Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment.

The incidence and severity of extrapyramidal symptoms are significantly less than with haloperidol. However, in some cases the following extrapyramidal symptoms may occur: tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia including oculogyric crisis. If acute in nature, these symptoms are usually mild and are reversible upon dose reduction and/or administration of antiparkinson medication, if necessary. In clinical trials in patients with acute mania risperidone treatment resulted in an incidence of EPS>10%. This is lower than the incidence observed in patients treated with classical neuroleptics.

Occasionally, orthostatic dizziness, hypotension including orthostatic, tachycardia including reflex tachycardia and hypertension have been observed following administration of risperidone.

Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea.

Weight gain, oedema and increased hepatic enzyme levels have been observed during treatment with risperidone.

A decrease in neutrophil and/or thrombocyte count has been reported.

As with classical neuroleptics, rare cases of the following have been reported in schizophrenic patients: water intoxication with hyponatraemia, either due to polydipsia or to the syndrome of inappropriate secretion of antidiuretic hormone; tardive dyskinesia, body temperature dysregulation and seizures.

Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.

Withdrawal reactions have been reported in association with antipsychotic drugs (see 4.4 Special warnings and special precautions for use).

4.9 Overdose

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, rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and 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 risperidone. 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

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 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, that 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 the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacokinetic properties

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. Food does not affect the absorption of risperidone from the stomach. The effect of food particles in the mouth on absorption has not been studied.

The most important route of metabolism of risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

A single-dose study showed higher active plasma concentrations and a slower elimination of risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

Risperidone Oral Solution is bio-equivalent to Risperidone tablets.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Malic acid
Hydroxypropylbetadex
Sodium methylparaben (E219)
Sodium saccharin
Disodium edetate
Potassium hydroxide
Purified water

6.2 Incompatibilities

Risperidone Oral Solution should only be diluted with those beverages listed in Posology and method of administration (see section 4.2).

6.3 Shelf life

The unopened bottles have a shelf life of 24 months. Once opened, the contents of the bottle should be used within three months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

125ml amber glass bottle containing 100ml of solution with 28 mm CRC CAP and press-in bottle adaptor and oral dispenser.

6.6 Special precautions for disposal and other handling

Each bottle is supplied with a press-in bottle adaptor and an oral dispenser.

Instructions for using the press-in bottle adaptor and an oral dispenser with Risperidone Oral Solution

a) Remove the child-resistant cap from the bottle by pushing down on the cap while turning it anti-clockwise. See fig 1.

b) Press the bottle adaptor firmly into the bottle neck.

c) Hold the empty dispenser and draw out the plunger to the required dose mark. See Fig 2.

d) Fit the dispenser into the bottle adaptor and turn the entire unit (bottle and oral dispenser) upside down.

e) To ensure the correct dose is obtained push the plunger in and then draw out medicine SLOWLY until the mark that matches the number of mg or ml to be taken is just visible. See Fig 3. If there are bubbles in the dispenser, repeat step d) until the bubbles are eliminated.

f) Place the bottle upright on a flat surface and remove the dispenser.

g) Make sure the patient is sitting or is held upright before giving the medicine.

h) Direct the dispenser towards the inside of the cheek. Push the plunger in slowly to give time to swallow; rapid squirting of the medicine may cause choking. The solution may also be emptied into a drink of mineral water, orange juice or black coffee.

i) Remove the dispenser from the adaptor and rinse the dispenser with some warm, soapy water.

Remove the bottle adaptor and replace the child-resistant cap on the bottle by screwing it down clockwise until it locks fully.

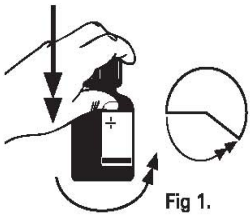

Fig 1.

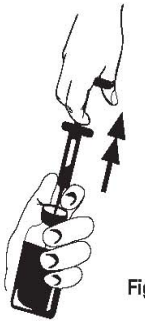

Fig 2.

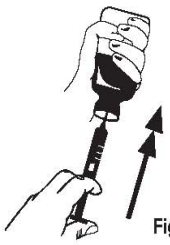

Fig 3.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham,
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 29831/0349

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/08/2008

10 DATE OF REVISION OF THE TEXT

20/08/2008

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER
RISPERIDONE 1mg/ml ORAL SOLUTION
Risperidone

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. WHAT RISPERIDONE ORAL SOLUTION IS AND WHAT IT IS USED FOR
Risperidone is one of a group of medicines called antipsychotics which are used to treat certain types of mental illnesses that can affect the way you think, feel, speak and behave. The symptoms of these illnesses include delusions, hallucinations (for example hearing or seeing things which are not there), unusual suspiciousness and becoming withdrawn. People suffering from these illnesses may also feel depressed, tense or anxious.

Risperidone is also used to treat the symptoms of bipolar disorder which include feeling "high" or excited, having excessive amounts of energy, needing less sleep than usual and being more talkative with racing thoughts.

2. BEFORE YOU TAKE RISPERIDONE ORAL SOLUTION
Do not take Risperidone Oral Solution if:
- you have ever had an allergic reaction to risperidone or any of the inactive ingredients of Risperidone Oral Solution (see 'Further information' section). An allergic reaction may be recognised as a rash, itching, swollen lips or face, or shortness of breath.

In clinical trials with risperidone, it was found that elderly patients with dementia (over 65 years) were three times more likely to experience side effects such as strokes or transient ischaemic attacks (temporary reduction of blood flow to the brain). In prescribing risperidone for you, your doctor will have considered that the benefits of treatment with this medicine outweigh the possible risks. If you experience sudden weakness or numbness of the face, arms or legs, slurred speech or problems with your vision, contact your doctor immediately.

Use of risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

Take special care with Risperidone Oral Solution if:
- you suffer from dementia
- you have Parkinson's disease
- you have liver or kidney disease
- you have heart or blood vessel disease
- you suffer from diabetes
- you suffer from epilepsy
- you have suffered a stroke or transient ischaemic attack, (temporary reduction in blood flow to the brain)
- you have high blood pressure
- you suffer from atrial fibrillation, a heart condition causing irregular rapid heart rhythm
- you smoke

If you suffer from any of the above speak to your doctor or pharmacist before taking Risperidone Oral Solution

Taking other medicines
It is very important that you inform your doctor if you are taking or have recently taken any other medicines, including those obtained without a prescription, as some medicines may affect the way Risperidone Oral Solution works.

In particular, tell your doctor if you are taking any of the following:
- levodopa, a drug used to treat Parkinson's disease
- carbamazepine, used to treat epilepsy
- furosemide, used to treat high blood pressure
- antidepressants such as fluoxetine and paroxetine
- tranquilisers, used to treat anxiety and to help you sleep
- painkillers

Taking Risperidone Oral Solution with food and drink
You should be careful how much alcohol you drink as the combined effect of risperidone and alcohol may make you feel drowsy.

Risperidone Oral Solution can be taken with or without food.

Pregnancy and breast-feeding
Do not take this medicine if you are pregnant or think you might be pregnant unless you have discussed this with your doctor first. Do not breast-feed while taking risperidone.

Driving and using machines
Risperidone might affect your alertness so you should not drive or operate machinery until the doctor sees how the solution affects you.

Important information about some of the ingredients of Risperidone Oral Solution
This medicinal product contains sodium methylparaben (E219), which may cause allergic reactions (possibly delayed).

3. HOW TO TAKE RISPERIDONE ORAL SOLUTION
Always take Risperidone Oral Solution exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Risperidone Oral Solution can be taken with or without food. The liquid can be swallowed directly or mixed with mineral water, orange juice or black coffee. Do not mix the solution with tea.

Instructions for using the dispenser and adaptor with Risperidone Oral Solution:
a) Remove the child-resistant cap from the bottle by pushing down on the cap while turning it anti-clockwise. See Fig 1.
b) Press the bottle adaptor firmly into the bottle neck.
c) Hold the empty dispenser and draw out the plunger to the required dose mark. See Fig 2.
d) Fit the dispenser into the bottle adaptor and turn the entire unit (bottle and oral dispenser) upside down.
e) To ensure the correct dose is obtained push the plunger in and then draw out medicine SLOWLY until the mark that matches the number of mg or ml to be taken is just visible. See Fig 3. If there are bubbles in the dispenser, repeat step d) until the bubbles are eliminated.
f) Place the bottle upright on a flat surface and remove the dispenser.
g) Make sure the patient is sitting or is held upright before giving the medicine.
h) Direct the dispenser towards the inside of the cheek. Push the plunger in slowly to give time to swallow; rapid squirting of the medicine may cause choking. The solution may also be emptied into a drink of mineral water, orange juice or black coffee.
i) Remove the dispenser from the adaptor and rinse the dispenser with some warm, soapy water.
j) Remove the bottle adaptor and replace the child-resistant cap on the bottle by screwing it down clockwise until it locks fully.

Your doctor will tell you how much Risperidone Oral Solution to take and for how long you should continue to take it.
This may vary from person to person – your doctor will adjust the amount of solution to suit you.
Remember – each millilitre (ml) of solution is equivalent to 1mg.

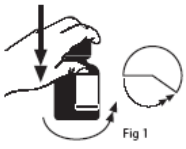
Fig 1


Fig 2

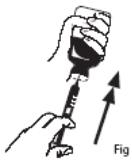
Fig 3

104020/1

pg 1/2

WOCKHARDT CREATIVE UNIT	CUSTOMER: CP PHARMA	PRODUCT: Risperidone 1mg/ml Oral Solution
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FILE NAME: Risperidone Liquid_Lit_104020-1.ai		ARTWORK (DETAILS) RECEIVED ON: 18th MARCH, 2008
SOFTWARE: ADOBE ILLUSTRATOR CS2		PROOF REVISION: ☑ 1st PDF sent on - 2ND APRIL 2008 ☑ 2nd PDF sent on - 24TH APRIL 2008 ☑ 3rd PDF sent on - 7TH MAY 2008 ☑ 4th PDF sent on - 9TH MAY 2008 ☑ 5th PDF sent on - 15TH MAY 2008 ☑ 6th PDF sent on - 16TH MAY 2008 ☑ 7th PDF sent on - 16TH JUNE 2008 ☑ 8th PDF sent on - 24TH JUNE 2008
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For adults and adolescents over 15 years of age with conditions which affect the way you think, feel, speak or behave:
The dose will be increased gradually over the first days of treatment as follows:
- Day 1 – 2mg (or 2ml)
- Day 2 – 4mg (or 4ml)

This will be taken as either a single dose or as half the dose in the morning and half the dose in the evening.
The dose will then be set depending on your needs but will usually be between 4mg (4ml) and 6mg (6ml) a day.

For adults and adolescents over 15 years of age with bipolar disorder:

A starting dose of 2mg (2ml) once a day is recommended. This may be increased to 6mg (6ml) per day depending on your requirements. Your doctor will tell you what dose is suitable for your situation.

For elderly patients or for those with liver or kidney disease

You should take half of the above doses. You will be told how much solution to take.

If you take more Risperidone Oral Solution than you should

If you take more Risperidone Oral Solution than you are supposed to, contact your doctor or nearest hospital Accident and Emergency Department. Do not attempt to drive or work with machinery.

If you forget to take Risperidone Oral Solution

If you forget to take a dose, take your next dose at the next correct time and continue your course. Do not take a double dose to make up for a forgotten dose.

If you stop taking Risperidone Oral Solution

Do not stop your treatment just because you feel better. It is important that you continue to take the solution for as long as the doctor has told you.

You should always check with your doctor before you stop treatment. Your doctor may want to reduce gradually the amount you are taking, especially if you have been taking a high dose. This will help to prevent a recurrence of the original trouble and reduce the chance of withdrawal effects such as feeling sick, vomiting, sweating, sleeplessness, muscle stiffness or jerky movements.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Risperidone Oral Solution can cause side effects, although not everybody gets them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Side effects that are common (affecting more than one person in every 10 people) include:
- difficulty in sleeping
- agitation or anxiety
- headache

Side effects that are less common (affecting up to nine people in every 100 people) include:
- sleepiness
- tiredness
- dizziness
- difficulty in concentrating
- blurred vision
- constipation
- indigestion
- feeling or being sick (nausea or vomiting)
- stomach ache
- sexual potency problems
- urinary incontinence (leakage of urine)
- runny or blocked nose
- liver problems
- local skin rash or swelling or other allergic reactions such as itching, swollen face or lips or shortness of breath
- weight gain or swelling of the ankles

Side effects that are rare (affecting up to nine people in 10 thousand people) include:
- breast swelling in men and women
- convulsions (fits)

Side effects that are very rare (affecting less than one person in 10 thousand people) include:
- excessive thirst or urination

If you experience any of the following, **stop taking Risperidone Oral Solution** and contact a doctor or the nearest hospital immediately:
- weakness or numbness of the face, arms or legs
- slurred speech
- trembling, muscle stiffness or spasm
- slowness of movement, excess saliva, restlessness or rolling of the eyes
- fever, fast breathing, sweating, muscle stiffness and reduced consciousness
- long lasting and painful erection

It is important to tell your doctor or pharmacist if you suffer from any of these or any other undesirable effects which are not listed above.

5. HOW TO STORE RISPERIDONE ORAL SOLUTION

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Risperidone Oral Solution after the expiry date which is stated on the bottle and the carton. The expiry date refers to the last day of the month. The solution should not be used for longer than three months after the bottle has been opened.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Risperidone Oral Solution contains

The active substance is risperidone. The solution contains 1mg of risperidone per millilitre (ml)

The solution also contains:

Malic acid, hydroxypropylbetadex, sodium methylparaben (E219), saccharin sodium, disodium edetate, potassium hydroxide and purified water.

What Risperidone Oral Solution looks like and contents of the pack

Risperidone Oral Solution is a clear, colourless oral solution. It is available in bottles containing 100ml. Each bottle is supplied with a press-in bottle adaptor and an oral dispenser.

Risperidone Oral solution - PIL Information

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:

0800 198 5000 (UK Only)

Please be ready to give the following information:

Product Name	Reference Number
Risperidone 1mg/ml Oral Solution	29831/0349

This is a service provided by the Royal National Institute of Blind People.

For the Republic of Ireland please call + 353 52 36253.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK
Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

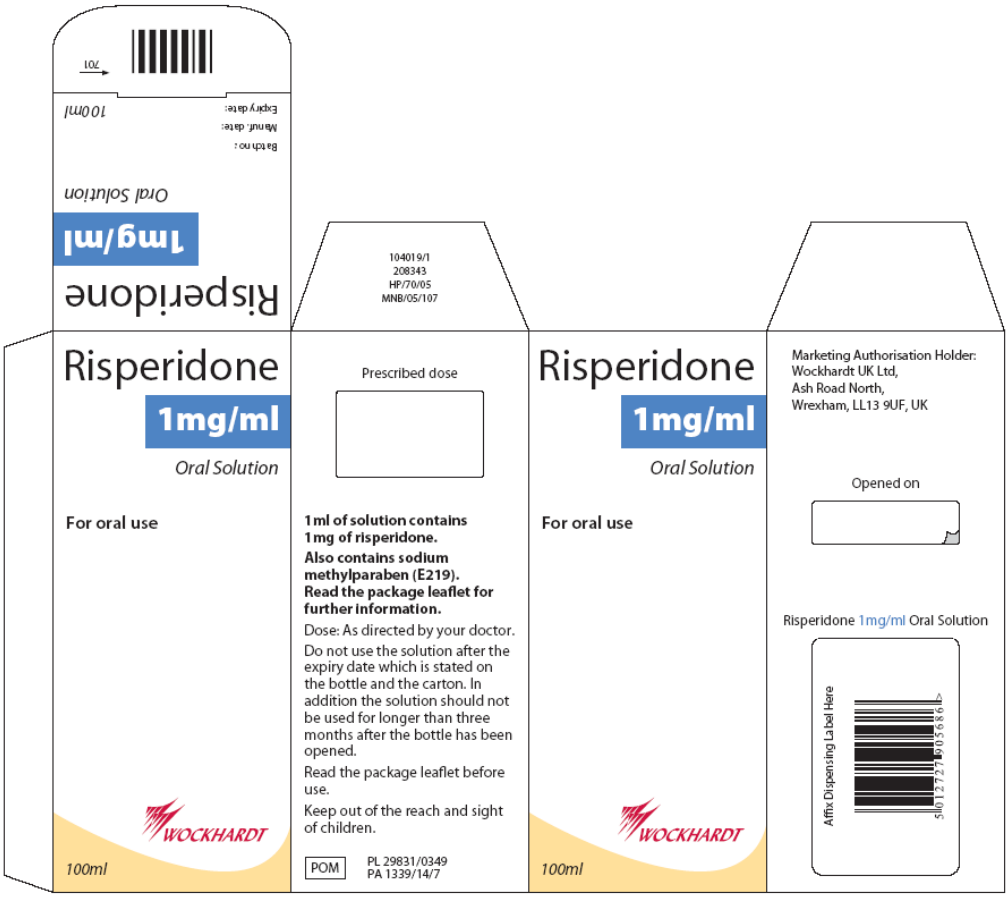
This medicinal product is authorised in the Member States of the EEA under the following names:
Ireland – Risperidone 1mg/ml Oral Solution

This leaflet was last approved in July 2008.

WOCKHARDT

104020/1
208342
HP/70/05
MNB/05/107

MODULE 4



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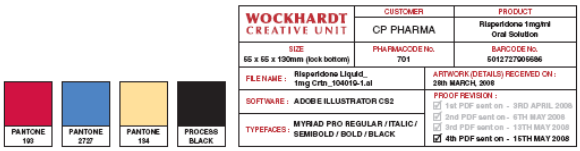


1ml of solution contains 1mg of risperidone.
Also contains sodium methylparaben (E219). Read the package leaflet for further information.

Dose: As directed by your doctor.

Do not use the solution after the expiry date which is stated on the packaging. In addition the solution should not be used for longer than three months after the bottle has been opened.

Read the package leaflet before use.

Keep out of the reach and sight of children.

PL 29831/0349 PA 1339/14/7

Opened on

Risperidone

1mg/ml

Oral Solution

104018/1 HP/70/05

For oral use

POM

Marketing Authorisation Holder:
Wockhardt UK Ltd,
Ash Road North,
Wrexham, LL13 9UF, UK

100ml

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Risperidone 1mg/ml oral solution, in the treatment of acute and chronic schizophrenic psychoses and for the treatment of mania in bipolar disorder, is approvable.

The application for Risperidone 1mg/ml oral solution is abridged application made according to Article 10(1) of Directive 2001/83/EC submitted within the Decentralised Procedure with the UK acting as the Reference Member State (RMS). The only Concerned Member State (CMS) is Ireland (IE). The reference medicinal product refer to Janssen-Cilag Ltd Risperdal Liquid (PL 00242/0199) for the 1mg/ml oral solution.

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 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, that 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 the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

The RMS has been assured that acceptable standards of GMP are in place for this product types at all sites responsible for the manufacture and assembly of this product.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Risperidone 1mg/ml oral solution
Name(s) of the active substance(s) (INN)	Risperidone
Pharmacotherapeutic classification (ATC code)	N05AX
Pharmaceutical form and strength(s)	1mg/ml oral solution
Reference numbers for the Mutual Recognition Procedure	UK/H/1174/01/DC
Reference Member State	United Kingdom
Member States Concerned	IE
Marketing Authorisation Number(s)	PL 29831/0349
Name and address of the authorisation holder	Wockhardt UK Limited, Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

DRUG SUBSTANCE

The active substance is the subject of DMF.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Active risperidone is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of three years is accepted and is supported by stability data.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely Disodium Edetate, purified water, Malic acid, Sodium Saccharin, Potassium Hydroxide, Sodium Methylparaben and Hydroxypropyl Betadex.

All excipients used comply with their respective European Pharmacopoeial monograph.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

Impurity profiles

Satisfactory information was provided on levels of impurities in the proposed product.

Manufacture

A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is packaged in amber glass bottle. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging comply with EU legislation regarding contact with solutions for parenteral and ophthalmic use Directive 2002/72/EC (as amended).

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with no storage conditions is set, which is satisfactory.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
It is recommended that Marketing Authorisation is granted for this application.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

PRE-CLINICAL ASPECTS

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASPECTS

1. INTRODUCTION

This is an outgoing Decentralised application for Risperidone 1mg/ml Oral Solution. This abridged standard application is submitted under Article 10(1) of Directive 2001/83/EC. The applicants Risperidone Oral solution claim equivalence to Risperdal Liquid, 1mg/ml (PL 00242/0199) first authorisation was granted to Janssen-Cilag Limited in the U.K. on 21st November 1995.

2. INDICATIONS

Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses 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. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone is indicated for the treatment of mania in bipolar disorder. 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 behaviours.

Risperidone is not licensed for the treatment of behavioural symptoms of dementia.

3. DOSE & DOSE SCHEDULE

1 ml of Risperidone Oral Solution contains 1 mg risperidone. If necessary Risperidone Oral Solution may be diluted with mineral water, orange juice or black coffee. When diluted in this way, the product should be used immediately. The liquid should not be mixed with tea.
(See Section 6. Pharmaceutical Particulars).

a Schizophrenia:
Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while risperidone therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating risperidone therapy in place of the next scheduled injection. The need for continuing existing antiparkinson medication should be re-evaluated periodically.

Adults
Risperidone Oral Solution may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day risperidone. The dosage may be increased to 4 mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.

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

Children
Use of risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

Renal and liver disease
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperidone should be used with caution in this group of patients until further experience is gained.

b Bipolar Mania:

Adults
Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.
As with all symptomatic treatments, the continued use of risperidone must be evaluated and justified on an ongoing basis.

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

Renal and liver disease
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.
Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers
There is limited information on the combined use of risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of risperidone producing lower plasma levels of the antipsychotic fraction of risperidone (see Section 4.5). It is therefore not recommended to co-administer risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of risperidone.

Method of administration
Oral use.

4. TOXICOLOGY

No new data.

5. CLINICAL PHARMACOLOGY

A randomised single, single dose, open-label, two-treatment, two-period, two-sequence, crossover comparative bioavailability study on Risperidone 1mg/ml oral solution (Wockhardt Limited India) compared with Risperidal Liquid (containing human subject under fasting condition).

Table No. 1 Investigational Product

Test product (A)	Risperidone 1mg/ml oral solution (Manufactured by; Wockhardt Limited, India)
Reference product (B)	Risperdal Liquid (Containing Risperidone 1mg/ml oral solution (Product Licence Holder: Janssen –Cilag Ltd UK

This was a two way crossover study of standard design in 12 subjects. All 12 subjects were included in the analyses and no issues were identified with the design or conduct of the study. Results were as follows:

Table No. 2a: Summary of PK & Statistical Results calculated for Risperidone in 12 subjects (01 to 12)

Parameters (unit)	Geometric Least Squares Mean N = 12			90 % Confidence Interval	Intra CV (%)	Power (%)
	Test (A)	Reference (B)	% Ratio (A/B)			
C_{max} (ng/mL)	9.2715	9.6929	95.65 %	84.79 % -107.91 %	16.40 %	85.70 %
AUC_{0-t} (ng.hr/mL)	60.7239	63.2291	96.04 %	85.68 % -107.64 %	15.51 %	89.13 %
$AUC_{0-\infty}$ (ng.hr/mL)	62.6491	65.0298	96.34 %	86.27 % -107.58 %	15.00 %	90.94 %

Figure No. 1a: Mean Plasma Concentration Time Curve for Risperidone

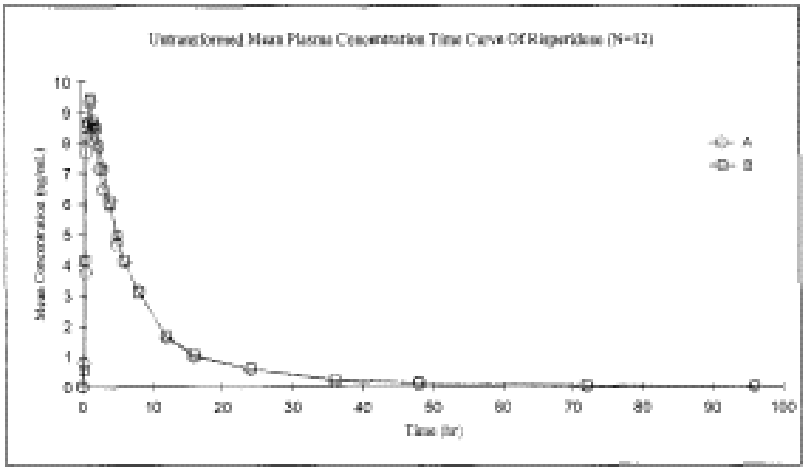
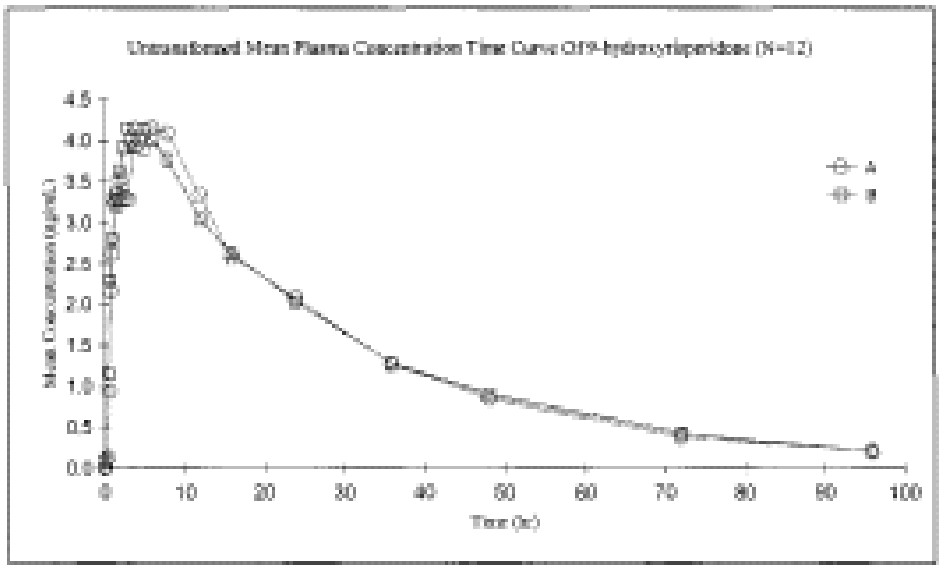


Table No. 2 b: Summary of PK & Statistical Results calculated for 9-hydroxyrisperidone in 12 subjects (01 to 12)

Parameters (unit)	Geometric Least Squares Mean N = 12			90 % Confidence Interval	Intra CV (%)	Power (%)
	Test (A)	Reference (B)	% Ratio (A/B)			
C_{max} (ng/mL)	3.6858	4.0201	91.69 %	76.13 % -110.41 %	25.52 %	47.97 %
AUC_{0-t} (ng.hr/mL)	112.3341	114.2734	98.30 %	89.27 % -108.25 %	13.08 %	96.13 %
$AUC_{0-\infty}$ (ng.hr/mL)	120.4917	122.3717	98.46 %	90.04 % -107.67 %	12.13 %	97.77 %

Figure No. 2a: Mean Plasma Concentration Time Curve for 9-hydroxyrisperidone

Figure No. 2a: Mean Plasma Concentration Time Curve for 9-hydroxyrisperidone



Bioequivalence was confirmed for the parent. Intra-individual variability was markedly higher for the metabolite and as a consequence 90% CIs for C_{max} were wide and fell outside 80-125%. However this is not of concern for the following reasons.

a. In the light of discussions at the EWP PK group the UK's current view is that it is not required that bioequivalence be shown for 9-OH risperidone, as kinetics are linear.
b. The study was powered to show bioequivalence for the parent not for the metabolite and the failure to meet the 80-125% criteria for C_{max} for 9-OH risperidone reflects this fact. The 90% CIs are wide and include unity. These results do not suggest a true difference between formulations.

In conclusion bioequivalence to the reference product has been established.

6. EFFICACY

No new data.

7. SAFETY

No new data.

8. EXPERT REPORTS

A satisfactory expert report is provided by an appropriately qualified physician.

9. PATIENT INFORMATION LEAFLET (PIL)

This is satisfactory.

10. LABELLING

Full colour mock-ups are provided. The labelling is medically satisfactory.

11. APPLICATION FORM (MAA)

The MAA is medically satisfactory.

12. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is satisfactory.

13. MEDICAL CONCLUSION

Marketing Authorisations may be granted for this application.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome

Annex 1

Reference: PL 29831/0349 - 0002
Product: Risperidone 1mg/ml Oral Solution
Marketing Authorisation Holder: Wockhardt UK Limited
Active Ingredient(s): Risperidone
EU Procedure Number: UK/H/1174/001/II/001

Reason:
To update sections 4 (Clinical particulars) and 5 (Pharmacological properties) of the Summary of Product Characteristics (SmPC), and consequentially the Patient Information Leaflet (PIL), in-line with the outcome of a Committee on Medicinal Products for Human Use (CHMP) Article 30 Harmonisation Referral Procedure.

In-line with the approved variation (application 0003), sections 4.4 and 4.8 of the SmPC have been further updated to include text related to venous thromboembolism (VTE). Furthermore, section 4.4 has been updated with text relating to 'increased mortality in elderly people and dementia' as agreed by the Pharmacovigilance Working Party (PhVWP) in October 2009. Changes to the SmPC are reflected in the PIL.

The design and layout of the mock up PIL approved with this variation is sufficiently similar to the current approved mock up PIL (which had undergone user testing). Further user testing was not considered necessary.

The approved PIL has a revision date of July 2011.

Supporting Evidence
A revised PIL and SmPC have been provided. The currently approved labelling is acceptable and needs no further revisions.

Evaluation
The amended sections of the SmPC and the amended PIL are satisfactory. These are provided below.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Risperidone is indicated for the treatment of schizophrenia.

Risperidone is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorder.

Risperidone is indicated for the short-term treatment (up to six weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.

Risperidone is indicated for the short-term symptomatic treatment (up to six weeks) of persistent aggression in conduct disorder in children from the age of five years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacological treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and

adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

4.2. Posology and method of administration

Schizophrenia:

Adults

Risperidone Oral Solution may be given once or twice daily.

Patients should start with 2 mg/day risperidone. The dosage may be increased on the second day to 4 mg. Subsequently the dosage can be maintained unchanged, or further individualised, 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 demonstrated superior efficacy to lower doses and may cause increased incidence of extrapyramidal symptoms. Safety of doses above 16 mg/day has not been evaluated, and are therefore not recommended.

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.

Paediatric population

Risperidone is not recommended for the use in children below age 18 with schizophrenia due to a lack of data on efficacy.

Manic episodes in bipolar disorder:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg risperidone. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. -Risperidone can be administered in flexible doses over a range of 1 to 6 mg per day to optimize each patient's level of efficacy and tolerability. Daily doses over 6mg risperidone have not been investigated in patients with manic episodes.

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

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. Since clinical experience in elderly is limited, caution should be exercised.

Paediatric population

Risperidone is not recommended for use in children below age 18 with bipolar mania due to a lack of data on efficacy.

Persistent aggression in patients with moderate to severe Alzheimer's dementia

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

Risperidone should not be used for more than 6 weeks in patients with persistent aggression in Alzheimer's dementia. During treatment, patients must be evaluated frequently and regularly, and the need for continuing treatment reassessed.

Conduct disorder

Children and adolescents from 5 to 18 years of age.

For subjects ≥50 kg, a starting dose of 0.5mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5mg once daily not more frequently than every other day, if needed. The optimum dose is 1mg once daily for most patients. Some patients,

however, may benefit from 0.5mg once daily while others may require 1.5mg once daily. For subjects <50kg, a starting does of 0.25mg once daily is recommended. This dosage can be individually adjusted by increments of 0.25mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5mg once daily for most patients. Some patients, however, may benefit from 0.25mg once daily while others may require 0.75mg once daily.

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

Risperidone is not recommended in children less than 5 years of age, as there is no experience in children less than 5 years of age with this disorder.

Renal and hepatic impairment
Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than in adults with normal renal function. 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.

Risperidone should be used with caution in these groups of patients.

Method of administration
Risperidone is for oral use. Food does not affect the absorption of risperidone.

Upon discontinuation, gradual withdrawal is advised. Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic medicines (see section 4.8). Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported.

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

For instructions on handling Risperidone Oral Solution, see section 6.6.

4.3. Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Elderly patients with dementia
Overall mortality
Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including risperidone. In placebo-controlled trials with risperidone in this population, the incidence of mortality was 4.0% for risperidone –treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7, 2.1). The mean age (range) of patients who died was 86 years (range 67-100).

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Risperidone is not licensed for the treatment of dementia-related behavioural disturbances.

Concomitant use with furosemide
In the risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

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

Cerebrovascular Adverse Events (CVAE)
In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with risperidone 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 CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34, 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Risperidone should be used with caution in patients with risk factors for stroke.

The risk of CVAEs was significantly higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia. Therefore, patients with other types of dementias than Alzheimer's should not be treated with risperidone.

Physicians are advised to assess the risks and benefits of the use of risperidone 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 CVAEs 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.

Risperidone should only be used short term for persistent aggression in patients with moderate to severe Alzheimer's dementia to supplement non-pharmacological approaches which have limited or no efficacy and when there is potential risk of harm to self or others.

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. Risperidone should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see section 4.2). A dose reduction should be considered if hypotension occurs.

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)
Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. The onset of extrapyramidal symptoms is a risk

factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

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

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including risperidone, to patients with Parkinson's disease or Dementia with Lewy Bodies (DLB). Parkinson's Disease may worsen with risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycaemia
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with risperidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Hyperprolactinaemia
Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Risperidone should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation
QT prolongation has very rarely been reported postmarketing. As with other antipsychotics, caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Seizures
Risperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism
Priapism may occur with risperidone treatment due to its alpha-adrenergic blocking effects.

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

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

Children and adolescents

Before risperidone is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands.

The sedative effect of risperidone should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of risperidone could improve the impact of the sedation on attention faculties of children and adolescents.

Risperidone was associated with mean increases in body weight and body mass index (BMI). Changes in height in the long-term open-label extension studies were within expected age-appropriate norms. The effect of long-term risperidone treatment on sexual maturation and height have not been adequately studied.

Because of the potential effects of prolonged hyperprolactinaemia on growth and sexual maturation in children and adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

During treatment with risperidone regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in children and adolescents see Section 4.2.

Excipients
Sodium methylparaben may cause delayed allergic reactions.

4.5. Interaction with other medicinal products and other forms of interaction

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g., class Ia antiarrhythmics (e.g., quinidine, dysopiramide, procainamide), class III antiarrhythmics (e.g., amiodarone, sotalol), tricyclic antidepressant (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistaminics, other antipsychotics, some antimalarials (i.e., chinice and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesiaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Potential for risperidone to affect other medicinal products
Risperidone should be used with caution in combination with other centrally-acting substances notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

Risperidone may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

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

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

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

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

Verapamil, an inhibitor of CYP 3A4 and P-gp, increases the plasma concentration of risperidone.

Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and on the active antipsychotic fraction.

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

The combined use of psychostimulants (e.g., methylphenidate) with risperidone in children and adolescents did not alter the pharmacokinetics and efficacy of risperidone.

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

Concomitant use of oral risperidone with paliperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive active antipsychotic fraction exposure.

4.6. Pregnancy and lactation

Pregnancy

There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. Consequently newborns should be monitored carefully. Risperidone was not teratogenic in animal studies but other types of reproductive toxicity were seen (see section 5.3). The potential risk for humans is unknown. Therefore, risperidone should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Lactation

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast milk in small quantities. There are no data available on adverse reactions in breast-feeding infants. Therefore, the advantage of breast-feeding should be weighed against the potential risks for the child.

4.7. Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) (incidence ≥10%) are: Parkinsonism, headache, and insomnia.

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

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

Adverse Drug Reactions by System Organ Class and Frequency

Investigations	
Common	Blood prolactin increased[a], weight increased
Uncommon	Electrocardiogram QT prolonged, electrocardiogram abnormal, blood glucose increased, transaminases increased, white blood cell count decreased, body temperature increased, eosinophil count increased, haemoglobin decreased, blood creatine phosphokinase increased
Rare	Body temperature decreased
Cardiac disorders	
Common	Tachycardia
Uncommon	Atrioventricular block, bundle branch block, atrial fibrillation, sinus bradycardia, palpitations
Blood and lymphatic system disorders	
Uncommon	Anaemia, thrombocytopenia
Rare	Granulocytopenia
Not known	Agranulocytosis
Nervous system disorders	
Very common	Parkinsonism[b], headache
Common	Akathisia[b], dizziness, tremor[b], dystonia[b], somnolence, sedation, lethargy, dyskinesia[b]
Uncommon	Unresponsive to stimuli, loss of consciousness, syncope, depressed level of consciousness, cerebrovascular accident, transient ischaemic attack, dysarthria, disturbance in attention, hypersomnia, dizziness postural, balance disorder, tardive dyskinesia, speech disorder, coordination abnormal, hypoaesthesia
Rare	Neuroleptic malignant syndrome, diabetic coma, cerebrovascular disorder, cerebral ischaemia, movement disorder
Eye disorders	
Common	Vision blurred
Uncommon	Conjunctivitis, ocular hyperaemia, eye discharge, eye swelling, dry eye, lacrimation increased, photophobia
Rare	Visual acuity reduced, eye rolling, glaucoma
Ear and labyrinth disorders	
Uncommon	Ear pain, tinnitus
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, epistaxis, cough, nasal congestion, pharyngolaryngeal pain
Uncommon	Wheezing, pneumonia aspiration, pulmonary congestion, respiratory disorder, rales, respiratory tract congestion, dysphonia
Rare	Sleep apnea syndrome, hyperventilation
Gastrointestinal disorders	
Common	Vomiting, diarrhoea, constipation, nausea, abdominal pain, dyspepsia, dry mouth, stomach discomfort
Uncommon	Dysphagia, gastritis, faecal incontinence, faecaloma
Rare	Intestinal obstruction, pancreatitis, lip swelling, cheilitis
Renal and urinary disorders	
Common	Enuresis
Uncommon	Dysuria, urinary incontinence, pollakiuria
Skin and subcutaneous tissue disorders	
Common	Rash, erythema
Uncommon	Angioedema, skin lesion, skin disorder, pruritus, acne, skin discolouration, alopecia, seborrhoeic dermatitis, dry skin, hyperkeratosis
Rare	Dandruff
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, back pain, pain in extremity
Uncommon	Muscular weakness, myalgia, neck pain, joint swelling, posture abnormal, joint stiffness, musculoskeletal chest pain

Rare	Rhabdomyolysis
Endocrine disorders	
Rare	Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	
Common	Increased appetite, decreased appetite
Uncommon	Anorexia, polydipsia
Very rare	Diabetic ketoacidosis
Not known	Water intoxication
Infections and infestations	
Common	Pneumonia, influenza, bronchitis, upper respiratory tract infection, urinary tract infection
Uncommon	Sinusitis, viral infection, ear infection, tonsillitis, cellulitis, otitis media, eye infection, localised infection, acarodermatitis, respiratory tract infection, cystitis, onychomycosis
Rare	Otitis media chronic
Vascular disorders	
Uncommon	Hypotension, orthostatic hypotension, flushing
Not known	Venous thromboembolism, including pulmonary embolism and deep vein thrombosis
General disorders and administration site conditions	
Common	Pyrexia, fatigue, peripheral oedema, asthenia, chest pain
Uncommon	Face oedema, gait disturbance, feeling abnormal, sluggishness, influenza like illness, thirst, chest discomfort, chills
Rare	Generalised oedema, hypothermia, drug withdrawal syndrome, peripheral coldness
Immune system disorders	
Uncommon	Hypersensitivity
Rare	Drug hypersensitivity
Not known	Anaphylactic reaction
Hepatobiliary disorders	
Rare	Jaundice
Reproductive system and breast disorders	
Uncommon	Amenorrhoea, sexual dysfunction, erectile dysfunction, ejaculation disorder, galactorrhoea, gynaecomastia, menstrual disorder, vaginal discharge
Not known	Priapism
Psychiatric disorders	
Very common	Insomnia
Common	Anxiety, agitation, sleep disorder
Uncommon	Confusional state, mania, libido decreased, listless, nervousness
Rare	Anorgasmia, blunted affect

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

[b] Extrapyramidal disorder may occur: Parkinsonism (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal),akathisia (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia. Dystonia includes dystonia, muscle spasms, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. Tremor includes tremor and parkinsonian rest tremor. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin.

The following is a list of additional ADRs associated with risperidone that have been identified as ADRs during clinical trials investigating a long acting injectable risperidone formulation but were not determined to be ADRs in the clinical trials investigating oral

risperidone. This table excludes those ADRs specifically associated with the formulation or injection route of administration of risperidone.

Additional Adverse Drug Reactions reported with injectable risperidone but not with oral risperidone by System Organ Class
Investigations
Weight decreased, Gamma-glutamyltransferase increased, Hepatic enzyme increased
Cardiac Disorders
Bradycardia
Blood and Lymphatic Disorders
Neutropenia
Nervous System Disorders
Paresthesia, Convulsion
Eye Disorders
Blepharospasm
Ear and Labyrinth Disorders
Vertigo
Gastrointestinal Disorders
Toothache, Tongue spasm
Skin and Subcutaneous Tissue Disorders
Eczema
Musculoskeletal, Connective Tissue, and Bone Disorders
Buttock pain
Infections and Infestations
Lower respiratory tract infection, Infection, Gastroenteritis, Subcutaneous abscess
Injury and Poisoning
Fall
Vascular Disorders
Hypertension
General Disorders and Administration Site Conditions
Pain
Psychiatric Disorders
Depression

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

Weight gain
The proportions of risperidone and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for risperidone (18%) compared to placebo (9%). In a pool of placebo-controlled 3-week studies in adult patients with acute mania, the incidence of weight increase of ≥ 7% at endpoint was comparable in the risperidone (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).

In a population of children and adolescents with conduct and other disruptive behaviour disorders, in long-term studies, weight increased by a mean of 7.3 kg after 12 months of treatment. The expected weight gain for normal children between 5-12 years of age is 3 to 5 kg per year. From 12-16 years of age, this magnitude of gaining 3 to 5 kg per year is maintained for girls, while boys gain approximately 5 kg per year.

Additional information on special populations
Adverse drug reactions that were reported with higher incidence in elderly patients with dementia or paediatric patients than in adult populations are described below:

Elderly patients with dementia
Transient ischaemic attack and cerebrovascular accident were ADRs reported in clinical trials with a frequency of 1.4% and 1.5%, respectively, in elderly patients with dementia. In addition, the following ADRs were reported with a frequency ≥5% in elderly patients with dementia and with at least twice the frequency seen in other adult populations: urinary tract infection, peripheral oedema, lethargy, and cough.

Paediatric patients
The following ADRs were reported with a frequency ≥5% in paediatric patients (5 to 17 years) and with at least twice the frequency seen in clinical trials in adults: somnolence/sedation, fatigue, headache, increased appetite, vomiting, upper respiratory tract infection, nasal congestion, abdominal pain, dizziness, cough, pyrexia, tremor, diarrhoea, and enuresis.

4.9. Overdose

Symptoms
In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsades de Pointes has been reported in association with combined overdose of risperidone and paroxetine.

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

Treatment
Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered only when the drug intake was less than one hour before. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to risperidone. 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 both serotonergic 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 antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Pharmacodynamic effects
Schizophrenia
The efficacy of risperidone in the short-term treatment of schizophrenia was established in four studies, 4- to 8-weeks in duration, which enrolled over 2500 patients who met DSM-IV criteria for schizophrenia. In a 6-week, placebo-controlled trial involving titration of risperidone in doses up to 10 mg/day administered twice daily, risperidone was superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score. In an 8-week, placebo-controlled trial involving four fixed doses of risperidone (2, 6, 10, and 16 mg/day, administered twice daily), all four risperidone groups were superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score. In an 8-week, dose comparison trial

involving five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day administered twice-daily), the 4, 8, and 16 mg/day risperidone dose groups were superior to the 1 mg risperidone dose group on PANSS total score. In a 4-week, placebo-controlled dose comparison trial involving two fixed doses of risperidone (4 and 8 mg/day administered once daily), both risperidone dose groups were superior to placebo on several PANSS measures, including total PANSS and a response measure (>20% reduction in PANSS total score). In a longer-term trial, adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medicinal product were randomised to risperidone 2 to 8 mg/day or to haloperidol for 1 to 2 years of observation for relapse. Patients receiving risperidone experienced a significantly longer time to relapse over this time period compared to those receiving haloperidol.

Manic episodes in bipolar disorder
The efficacy of risperidone monotherapy in the acute treatment of manic episodes associated with bipolar I disorder was demonstrated in three double-blind, placebo-controlled monotherapy studies in approximately 820 patients who had bipolar I disorder, based on DSM-IV criteria. In the three studies, risperidone 1 to 6 mg/day (starting dose 3 mg in two studies and 2 mg in one study) was shown to be significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in total Young Mania RatingScale (YMRS) score at Week 3. Secondary efficacy outcomes were generally consistent with the primary outcome. The percentage of patients with a decrease of ≥ 50% in total YMRS score from baseline to the 3-week endpoint was significantly higher for risperidone than for placebo. One of the three studies included a haloperidol arm and a 9-week double-blind maintenance phase. Efficacy was maintained throughout the 9-week maintenance treatment period. Change from baseline in total YMRS showed continued improvement and was comparable between risperidone and haloperidol at Week 12.

The efficacy of risperidone in addition to mood stabilisers in the treatment of acute mania was demonstrated in one of two 3-week double-blind studies in approximately 300 patients who met the DSM-IV criteria for bipolar I disorder. In one 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day in addition to lithium or valproate was superior to lithium or valproate alone on the pre-specified primary endpoint, i.e., the change from baseline in YMRS total score at Week 3. In a second 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day, combined with lithium, valproate, or carbamazepine was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this study was induction of risperidone and 9-hydroxy-risperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxy-risperidone. When the carbamazepine group was excluded in a post-hoc analysis, risperidone combined with lithium or valproate was superior to lithium or valproate alone in the reduction of YMRS total score.

Persistent aggression in dementia
The efficacy of risperidone in the treatment of Behavioural and Psychological Symptoms of Dementia (BPSD), which includes behavioural disturbances, such as aggressiveness, agitation, psychosis, activity, and affective disturbances was demonstrated in three double-blind, placebo-controlled studies in 1150 elderly patients with moderate to severe dementia. One study included fixed risperidone doses of 0.5, 1, and 2 mg/day. Two flexible-dose studies included risperidone dose groups in the range of 0.5 to 4 mg/day and 0.5 to 2 mg/day, respectively. Risperidone showed statistically significant and clinically important effectiveness in treating aggression and less consistently in treating agitation and psychosis in elderly dementia patients (as measured by the Behavioural Pathology in Alzheimer's Disease Rating Scale [BEHAVE-AD] and the Cohen-Mansfield Agitation Inventory [CMAI]). The treatment effect of risperidone was independent of Mini-Mental State Examination (MMSE) score (and consequently of the severity of dementia); of sedative properties of risperidone; of the presence or absence of psychosis; and of the type of dementia, Alzheimer's, vascular, or mixed. (See also section 4.4)

Conduct disorder
The efficacy of risperidone in the short-term treatment of disruptive behaviours was demonstrated in two double-blind placebo-controlled studies in approximately 240 patients 5

to 12 years of age with a DSM-IV diagnosis of disruptive behaviour disorders (DBD) and borderline intellectual functioning or mild or moderate mental retardation/learning disorder. In the two studies, risperidone 0.02 to 0.06 mg/kg/day was significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in the Conduct Problem subscale of the Nisonger-Child Behaviour Rating Form (N-CBRF) at Week 6.

5.2. Pharmacokinetic properties

Risperidone oral solution is bioequivalent to risperidone film-coated tablets.

Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone (see *Biotransformation and Elimination*).

Absorption
Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) compared with a solution. The absorption is not affected by food and thus risperidone can be given with or without meals. 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.

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

Biotransformation and elimination
Risperidone is metabolised by CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. CYP 2D6 is subject to genetic polymorphism. Extensive CYP 2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP 2D6 metabolisers convert it much more slowly. Although extensive metabolisers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolisers, the pharmacokinetics of risperidone and 9-hydroxy-risperidone combined (i.e., the active antipsychotic fraction), after single and multiple doses, are similar in extensive and poor metabolisers of CYP 2D6.

Another metabolic pathway of risperidone is N-dealkylation. In vitro studies in human liver microsomes showed that risperidone at clinically relevant concentration does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP 1A2, CYP 2A6, CYP 2C8/9/10, CYP 2D6, CYP 2E1, CYP 3A4, and CYP 3A5. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the dose. The remainder is inactive metabolites. 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.

Linearity
Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

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

Paediatric patients

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

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

5.3. Preclinical safety data

In (sub)chronic toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependant 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 addition, tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Risperidone was not teratogenic in rat and rabbit. In rat reproduction studies with risperidone, adverse effects were seen on mating behaviour of the parents, and on the birth weight and survival of the offspring. In rats, intrauterine exposure to risperidone was associated with cognitive deficits in adulthood. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring. Risperidone was not genotoxic in a battery of tests. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D_2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown. In vitro and in vivo, animal models show that at high doses risperidone may cause QT interval prolongation, which has been associated with a theoretically increased risk of torsade de pointes in patients.

PACKAGE LEAFLET: INFORMATION FOR THE USER

RISPERIDONE 1mg/ml ORAL SOLUTION

Risperidone

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. WHAT RISPERIDONE ORAL SOLUTION IS AND WHAT IT IS USED FOR

Risperidone is one of a group of medicines called antipsychotics.

Risperidone is used to treat the following:
- Schizophrenia, where you may see, hear or feel things that are not there, believe things that are not true or feel unusually suspicious, or confused.
- Mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called "bipolar disorder".
- Short-term treatment (up to six weeks) of long-term aggression in people with Alzheimer's dementia, who harm themselves or others. Alternative (non-drug) treatments should have been used previously.
- Short-term treatment (up to six weeks) of long-term aggression in intellectually disabled children (at least five years of age) and adolescents with conduct disorder.

2. BEFORE YOU TAKE RISPERIDONE ORAL SOLUTION

Do not take Risperidone Oral Solution if:
- you are allergic (hypersensitive) to risperidone or any of the other ingredients of Risperidone Oral Solution (see 'Further information' section).

If you are not sure if the above applies to you, talk to your doctor or pharmacist before using Risperidone Oral Solution.

Take special care with Risperidone Oral Solution:

Check with your doctor or pharmacist before taking Risperidone Oral Solution if:
- you have a heart problem. Examples include an irregular heart rhythm or if you are prone to low blood pressure or if you are using medicines for your blood pressure. Risperidone Oral Solution may cause low blood pressure. Your dose may need to be adjusted.
- you know of any factors which would favour you having a stroke, such as high blood pressure, cardiovascular disorder or blood vessel problems in the brain
- you have Parkinson's disease or dementia
- you have liver problems
- you have kidney problems
- you suffer from diabetes
- you suffer from epilepsy
- You are a man and you have ever had a prolonged or painful erection. If you experience this while taking Risperidone Oral Solution, contact your doctor straight away
- you have problems controlling your body temperature or overheating
- you have an abnormally high level of the hormone prolactin in your blood or if you have a tumour, which is possibly dependent on prolactin
- you or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.

Tell your doctor immediately if you experience
- involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of risperidone may be needed
- fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called "neuroleptic malignant syndrome"). Immediate medical treatment may be needed.

If you are not sure if any of the above applies to you, speak to your doctor or pharmacist before taking Risperidone Oral Solution.

Risperidone Oral Solution may cause you to gain weight.

Elderly people with dementia
In elderly patients with dementia, there is an increased risk of stroke. You should not take risperidone if you have dementia caused by stroke.

During treatment with risperidone you should frequently see your doctor.

Medical treatment should be sought straight away if you or your care-giver notice a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke.

Children and adolescents
Before treatment is started in conduct disorder, other causes of aggressive behaviour should have been ruled out.

If during treatment with risperidone tiredness occurs, a change in the time of administration might improve attention difficulties.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal medicines.

It is especially important to talk to your doctor or pharmacist if you are taking any of the following:
- medicines that work on your brain to help you calm down (benzodiazepines) or some medicines for pain (opiates), medicines for allergy (some antihistamines), as risperidone may increase the sedative effect of all of these
- medicines that may change the electrical activity of your heart, such as medicines for malaria, heart rhythm problems (such as quinidine), allergies (antihistamines), some antidepressants or other medicines for mental health problems
- medicines that cause a slow heart beat
- medicines that cause low blood potassium (e.g. certain diuretics)
- medicines to treat elevated blood pressure. Risperidone can lower blood pressure
- medicines for Parkinson's disease (such as levodopa)
- water tablets (diuretics) used for heart problems or swelling of parts of your body due to a build up of too much fluid (such as furosemide or chlorothiazide). Risperidone taken by itself or with furosemide, may have an increased risk of stroke or death in elderly people with dementia

The following medicines may reduce the effect of risperidone:
- rifampicin (a medicine for treating some infections)
- carbamazepine, phenytoin (medicines for epilepsy)
- phenobarbital

If you start or stop taking such medicines you may need a different dose of risperidone

The following medicines may increase the effect of risperidone:
- quinidine (used for certain types of heart disease)
- antidepressants such as paroxetine, fluoxetine, tricyclic antidepressants
- medicines known as beta blockers (used to treat high blood pressure)
- phenothiazines (e.g. used to treat psychosis or to calm down)
- cimetidine, ranitidine (blockers of the acidity of the stomach)

If you start or stop taking such medicines you may need a different dose of risperidone

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using risperidone.

Taking Risperidone Oral Solution with food and drink
You should be careful how much alcohol you drink as the combined effect of risperidone and alcohol may make you feel drowsy.

Risperidone Oral Solution can be taken with or without food.

Pregnancy and breast-feeding
- talk to your doctor before using Risperidone Oral Solution if you are pregnant, trying to become pregnant or are breast-feeding. Your doctor will decide if you can take it
- shaking, muscle stiffness and problems feeding, all of which are reversible, have been seen in newborn babies when risperidone was used during the last trimester of pregnancy.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Dizziness, tiredness, and vision problems may occur during treatment with Risperidone Oral Solution. Do not drive or use any tools or machines without talking to your doctor first.

Important information about some of the ingredients of Risperidone Oral Solution
This medicinal product contains sodium methylparaben (E219), which may cause allergic reactions (possibly delayed).

3. HOW TO TAKE RISPERIDONE ORAL SOLUTION

How much to take

For the treatment of schizophrenia
Adults
- The usual starting dose is 2mg per day, this may be increased to 4mg per day on the second day
- Your dose may then be adjusted by your doctor depending on how you respond to the treatment
- Most people feel better with daily doses of 4 to 6mg
- This total daily dose can be divided into either one or two doses a day. Your doctor will tell you which is best for you.

Elderly people
- Your starting dose will normally be 0.5mg twice a day
- Your dose may then be gradually increased by your doctor to 1mg to 2mg twice a day
- Your doctor will tell you which is the best for you

Children and adolescents
- Children and adolescents under 18 years old should not be treated with Risperidone Oral Solution for schizophrenia

For the treatment of mania
Adults
- Your starting dose will usually be 2mg once a day
- Your dose may then be gradually adjusted by your doctor depending on how you respond to the treatment
- Most people feel better with doses of 1 to 6mg once a day

Elderly people
- Your starting dose will usually be 0.5mg twice a day
- Your dose may then be gradually adjusted by your doctor to 1mg to 2 mg twice a day depending on how much you respond to the treatment.

Children and adolescents
- Children and adolescents under 18 years old should not be treated with Risperidone Oral Solution for bipolar mania.

For the treatment of long-standing aggression in people with Alzheimer's dementia
Adults (including elderly people)
- Your starting dose will normally be 0.25mg twice a day
- Your dose may then be gradually adjusted by your doctor depending on how you respond to the treatment
- Most people feel better with 0.5mg twice a day. Some patients may need 1mg twice a day
- Treatment duration in patients with Alzheimer's dementia should be not more than six weeks

For the treatment of conduct disorder in children and adolescents
The dose will depend on your child's weight

For children who weigh less than 50kg
- The starting dose will normally be 0.25mg once a day
- The dose may be increased every other day in steps of 0.25mg per day
- The usual maintenance dose is 0.25mg to 0.75mg once a day

For children who weigh 50kg or more
- The starting dose will normally be 0.5mg once a day
- The dose may be increased every other day in steps of 0.5mg per day
- The usual maintenance dose is 0.5mg to 1.5mg once a day

Treatment duration in patients with conduct disorder should not be more than six weeks.

Children under 5 years old should not be treated with Risperidone Oral Solution for conduct disorder.

People with kidney or liver problems
Regardless of the disease to be treated, all starting doses and following doses of risperidone should be halved. Dose increase should be slower in these patients.

Risperidone should be used with caution in this patient group.

How to take Risperidone Oral Solution
Always take Risperidone Oral Solution exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will tell you how much medicine to take and for how long. This will depend on your condition and varies from person to person. The amount of medicine you should take is explained under the 'How much to take' sub-heading above.

Instructions for using the dispenser and adaptor with Risperidone Oral Solution:
a) Remove the child-resistant cap from the bottle by pushing down on the cap while turning it anti-clockwise. See Fig 1.
b) Press the bottle adaptor firmly into the bottle neck.

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c) Hold the empty dispenser and draw out the plunger to the required dose mark. See Fig 2.
d) Fit the dispenser into the bottle adaptor and turn the entire unit (bottle and oral dispenser) upside down.
e) To ensure the correct dose is obtained push the plunger in and then draw out medicine SLOWLY until the mark that matches the number of mg or ml to be taken is just visible. See Fig 3. If there are bubbles in the dispenser, repeat step d) until the bubbles are eliminated.
f) Place the bottle upright on a flat surface and remove the dispenser.
g) Make sure the patient is sitting or is held upright before giving the medicine.
h) Direct the dispenser towards the inside of the cheek. Push the plunger in slowly to give time to swallow; rapid squirting of the medicine may cause choking. The solution may also be emptied into a drink of mineral water, orange juice or black coffee.
i) Remove the dispenser from the adaptor and rinse the dispenser with some warm, soapy water.
j) Remove the bottle adaptor and replace the child-resistant cap on the bottle by screwing it down clockwise until it locks fully.


Fig 1


Fig 2


Fig 3

If you take more Risperidone Oral Solution than you should
- See a doctor right away. Take the medicine pack with you
- In case of overdose you may feel sleepy or tired, or have abnormal body movements, problems standing and walking, feel dizzy due to low blood pressure, or have abnormal heart beats or fits.

If you forget to take Risperidone Oral Solution
- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual. If you miss two or more doses, contact your doctor
- **Do not take a double dose (two doses at the same time) to make up for a forgotten dose**

If you stop taking Risperidone Oral Solution
You should not stop taking this medicine unless told to do so by your doctor. Your symptoms may return. If your doctor decides to stop this medicine, your dose may be decreased gradually over a few days.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Risperidone Oral Solution can cause side effects, although not everybody gets them.

The following side-effects may happen:
- Blood clots in the veins especially in the legs(symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.

Side effects that are very common (affecting more than one person in every 10 people):
- Parkinsonism. This is a medical term that includes many symptoms. Each individual symptom may occur less frequently than in one in 10 people. Parkinsonism includes: increase in saliva secretion or watery mouth, musculoskeletal stiffness, drooling, jerks when bending the limbs, slow, reduced or impaired body movements, no expression on the face, muscle tightness, stiff neck, muscle stiffness, small, shuffling, hurried steps and lack of normal arm movements when walking, persistent blinking in response to tapping of the forehead (an abnormal reflex)
- Headache, difficulty falling or staying asleep

Side effects that are common (affecting one to ten people in every 100 people):
- Drowsiness, fatigue, restlessness, inability to sit still, irritability, anxiety, sleepiness, dizziness, poor attention, feeling exhausted, sleep disorder
- Vomiting, diarrhoea, constipation, nausea, increased appetite, abdominal pain or discomfort, sore throat, dry mouth
- Weight increased, increase in body temperature, decreased appetite
- Difficulty breathing, lung infection (pneumonia), flu, infection of the breathing passages, blurred vision, nose congestion, nose bleeding, cough
- Urinary tract infection, bed wetting
- Muscle spasm, involuntary movements of face or arms and legs, joint pain, back pain, swelling of arms and legs, pain in arms and legs
- Rash, skin redness
- Fast beating heart, chest pain
- Blood prolactin hormone level increased.

Side effects that are uncommon (affecting one to 10 people in one thousand people):
- Excessive drinking of water, stool incontinence, thirsty, very hard faeces, hoarseness or voice disorder
- Lung infection caused by inhaling of food into the breathing passages, bladder infection, 'pink eye', sinus infection, viral infection, ear infection, tonsil infection, infection under the skin, eye infection, stomach infection, eye discharge, yeast infection of nails
- Abnormal electrical conduction of the heart, drop in blood pressure after standing, low blood pressure, feeling dizzy after changing body position, abnormal electric activity tracing of the heart (ECG), abnormal heart rhythm, awareness of heart beating, heart rate increased or decreased
- Urinary incontinence, pain when passing urine, frequent passing of urine
- Confused, disturbance in attention, low level of consciousness, excessive sleep, nervousness, elated mood (mania) , lack of energy and interest
- Blood sugar increased, liver enzymes increased, white blood cell count decreased, low haemoglobin or red blood cell count (anaemia), increase in eosinophils (special white blood cells), blood creatinine phosphokinase increased, decrease in platelets (blood cells that help you stop bleeding)
- Muscle weakness, muscle pain, ear pain, neck pain, joint swelling, abnormal posture, joint stiffness, musculoskeletal chest pain, chest discomfort
- Skin lesion, skin disorder, dry skin, intense itching of skin, acne, hair loss, skin inflammation caused by mites, skin discoloration, thickening of skin, flushing, reduced skin sensitivity to pain or touch, inflammation of oily skin
- No menstruation, sexual dysfunction, erectile dysfunction, ejaculation disorder, breast discharge, enlargement of breast in men, decreased sexual drive, irregular menstruation, vaginal discharge
- Fainting, gait disturbance, sluggishness, decreased appetite resulting in malnutrition and low body weight, feeling 'out of sorts', balance disorder, allergy, edema, speech disorder, chills, abnormal coordination
- Painful oversensitivity to light, increased blood flow to the eye, eye swelling, dry eye, increase in tears
- Breathing passage disorder, lung congestion, crackly lung noise, congestion of breathing passages, trouble speaking, difficulty swallowing, cough with sputum, coarse/whistling sound during breathing, flu-like illness, sinus congestion
- Unresponsive to stimuli, loss of consciousness, sudden swelling of lips and eyes along with difficulty breathing, sudden weakness or numbness of the face, arms, or legs, especially on one side, or instances of slurred speech that last for less than 24 hours (these are called mini-strokes or strokes), involuntary movements of face, arms, or legs, ringing in ears, face edema.

Side effects that are rare (affecting one to 10 people in 10 thousand people):
- Inability to reach orgasm, menstrual disorder
- Dandruff
- Drug allergy, coldness in arms and legs, lip swelling, lip inflammation
- Glaucoma, reduced visual clarity, eyelid margin crusting, eye rolling
- Lack of emotion
- Change in consciousness with increased body temperature and twitching of muscles, edema all over the body, drug withdrawal syndrome, body temperature decreased
- Fast shallow breathing, trouble breathing during sleep, chronic otitis media
- Obstruction of intestine
- Reduced blood flow to the brain
- Decrease in white blood cells, inappropriate secretion of a hormone that controls urine volume
- Breakdown of muscle fibres and pain in muscles (rhabdomyolysis), movement disorder
- Coma due to uncontrolled diabetes
- Yellowing of the skin and the eyes (jaundice)
- Inflammation of the pancreas.

Side effects that are very rare (affecting less than one person in 10 thousand people):
- Life threatening complications of uncontrolled diabetes.

Side effects with unknown frequency of occurrence (frequency cannot be estimated from available data):
- Severe allergic reaction resulting in difficulty in breathing and shock
- No granulocytes (a type of white blood cell to help you against infection)
- Prolonged and painful erection
- Dangerously excessive intake of water
- In elderly people with dementia, a small increase in the number of deaths has been reported for patients taking antipsychotics compared with those not receiving antipsychotics.

Long acting injection formulation of risperidone
The following side effects have been reported with the use of a long acting injection formulation of risperidone. Even if you are not being treated with long acting injections of risperidone but you experience any of the following, talk to your doctor.
- Infection of the intestine
- Abscess under the skin, tingling pricking or numbness of skin, inflammation of the skin
- Decrease in white blood cell counts that helps to protect you against bacterial infection
- Depression
- Convulsion
- Eye blinking
- Sensation of spinning or swaying
- Slow beating heart, high blood pressure
- Toothache, tongue spasm
- Buttock pain
- Weight decreased.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE RISPERIDONE ORAL SOLUTION

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Risperidone Oral Solution after the expiry date which is stated on the bottle and the carton. The expiry date refers to the last day of the month. The solution should not be used for longer than three months after the bottle has been opened.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Risperidone Oral Solution contains
The active substance is risperidone. The solution contains 1mg of risperidone per millilitre (ml)

The solution also contains:
Malic acid, hydroxypropylbetadex, sodium methylparaben (E219), saccharin sodium, disodium edetate, potassium hydroxide and purified water.

What Risperidone Oral Solution looks like and contents of the pack
Risperidone Oral Solution is a clear, colourless oral solution. It is available in bottles containing 100ml. Each bottle is supplied with a press-in bottle adaptor and an oral dispenser.

Risperidone Oral solution - PIL Information
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:
0800 198 5000 (UK Only)

Please be ready to give the following information:

Product Name	Reference Number
Risperidone 1mg/ml Oral Solution	29831/0349

This is a service provided by the Royal National Institute of Blind People.
For the Republic of Ireland please call + 353 52 36253.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK
Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

This medicinal product is authorised in the Member States of the EEA under the following names:
Ireland – Risperidone 1mg/ml Oral Solution

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