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 The symptoms of these illnesses include delusions, hallucinations, unusual suspiciousness and becoming withdrawn.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

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<td><strong>Active Substance</strong></td>
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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 psy
chotic 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
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-HT2 and dopaminergic D2 receptors. Risperidone binds also to alphao-adrenergic receptors and, with lower affinity, to H1-histaminergic and alapho-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical 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 anticlockwise. 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.
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/08/2008

10 DATE OF REVISION OF THE TEXT
20/08/2008
Module 3

Risperidone 1mg/ml Oral Solution

In this leaflet:
1. What Risperidone Oral Solution is and what it is used for
2. Before you take Risperidone Oral Solution
3. How to take Risperidone Oral Solution
4. Possible side effects
5. How to stop taking Risperidone Oral Solution
6. Further information

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

Risperidone is used in the treatment of schizophrenia and bipolar disorder.

2. BEFORE YOU TAKE RISPERIDONE ORAL SOLUTION

Do not take Risperidone Oral Solution if:
- you have had an allergic reaction to Risperidone or any of the other ingredients of Risperidone Oral Solution (see Further Information section).
- you have a heart condition (severe palpitations, or a history of heart attack)
- you have any visible signs of meningococcal disease
- you have had a stroke (severe headache, or a history of stroke)
- you have high blood pressure
- you have high blood pressure or you are taking any medicines for high blood pressure
- you have a history of kidney disease
- you have liver disease
- you have had a bone marrow transplant
- you have a history of diabetes

3. HOW TO TAKE RISPERIDONE ORAL SOLUTION

Always take Risperidone Oral Solution exactly as your doctor tells you. The recommended starting dose for adults is usually 1mg to 2mg per day and then gradually increased.

4. POSSIBLE SIDE EFFECTS

Some common side effects of Risperidone include:
- weight gain
- constipation
- dry mouth
- raised blood glucose levels
- raised cholesterol levels

5. HOW TO STOP TAKING RISPERIDONE ORAL SOLUTION

If you think you have taken too much of Risperidone Oral Solution, contact your doctor or local hospital straight away.

6. FURTHER INFORMATION

Risperidone Oral Solution is a medicine that is usually taken once or twice a day. It is important to talk to your doctor about how much you should take and how often.

Read the full leaflet before you start taking Risperidone Oral Solution.

Fig 1: This is a diagram showing how to open the bottle and pour the solution into the cup. The instructions are as follows:
- Hold the bottle with the nozzle facing upwards.
- Press the nozzle to release the solution.
- Pour the solution into a cup.

Fig 2: This is a diagram showing how to use the measuring cup. The instructions are as follows:
- Hold the cup over the sink.
- Gently pour the solution into the cup.
- Discard the cup according to local regulations.

Fig 3: This is a diagram showing how to store the bottle. The instructions are as follows:
- Keep the bottle in a cool, dry place.
- Do not freeze the bottle.

Fig 4: This is a diagram showing how to use the syringe. The instructions are as follows:
- Hold the syringe with the needle facing upwards.
- Insert the needle into the solution.
- Suck up the solution until the syringe is full.

Fig 5: This is a diagram showing how to use the injection. The instructions are as follows:
- Hold the syringe with the needle facing downwards.
- Insert the needle into the muscle.
- Squeeze the plunger to inject the solution.

Fig 6: This is a diagram showing how to use the inhaler. The instructions are as follows:
- Hold the inhaler with the mouthpiece facing upwards.
- Take a deep breath in.
- Press the button to release the medication.
- Hold your breath for 5 seconds.
- Take another deep breath.

Fig 7: This is a diagram showing how to use the patch. The instructions are as follows:
- Clean the skin with alcohol.
- Peel the backing off the patch.
- Apply the patch to the skin.
- Remove the patch after 72 hours.

Fig 8: This is a diagram showing how to use the lozenge. The instructions are as follows:
- Place the lozenge on the tongue.
- Let it dissolve naturally.
- Do not swallow.

Fig 9: This is a diagram showing how to use the capsule. The instructions are as follows:
- Open the capsule.
- Pour the contents into a cup.
- Drink the solution.

Fig 10: This is a diagram showing how to use the tablet. The instructions are as follows:
- Chew the tablet before swallowing.
- Do not cut or crush the tablet.

Fig 11: This is a diagram showing how to use the cream. The instructions are as follows:
- Apply a thin layer to the affected area.
- Rub in gently.
- Wash your hands after use.

Fig 12: This is a diagram showing how to use the gel. The instructions are as follows:
- Apply a thin layer to the affected area.
- Rub in gently.
- Wash your hands after use.

Fig 13: This is a diagram showing how to use the liquid. The instructions are as follows:
- Take the prescribed dose.
- Drink plenty of water.
- Do not exceed the recommended dose.

Fig 14: This is a diagram showing how to use the mouthwash. The instructions are as follows:
- Swish the solution around in your mouth.
- Spit it out.
- Do not rinse your mouth.

Fig 15: This is a diagram showing how to use the ointment. The instructions are as follows:
- Apply a thin layer to the affected area.
- Cover with a sterile dressing.
- Wash your hands after use.

Fig 16: This is a diagram showing how to use the suppository. The instructions are as follows:
- Lie down on your back.
- Insert the suppository into the rectum.
- Lie down for 30 minutes.

Fig 17: This is a diagram showing how to use the enema. The instructions are as follows:
- Lie down on your back.
- Insert the enema into the rectum.
- Lie down for 30 minutes.

Fig 18: This is a diagram showing how to use the eye drops. The instructions are as follows:
- Hold the bottle tilted upwards.
- Press the nozzle to release the solution into your eye.
- Do not use the drops if they are overdue.

Fig 19: This is a diagram showing how to use the ear drops. The instructions are as follows:
- Hold the bottle tilted upwards.
- Press the nozzle to release the solution into your ear.
- Do not use the drops if they are overdue.

Fig 20: This is a diagram showing how to use the nose drops. The instructions are as follows:
- Hold the bottle tilted upwards.
- Press the nozzle to release the solution into your nose.
- Do not use the drops if they are overdue.

Fig 21: This is a diagram showing how to use the rectal gel. The instructions are as follows:
- Lie down on your back.
- Insert the gel into the rectum.
- Lie down for 30 minutes.

Fig 22: This is a diagram showing how to use the rectal suppository. The instructions are as follows:
- Lie down on your back.
- Insert the suppository into the rectum.
- Lie down for 30 minutes.

Fig 23: This is a diagram showing how to use the vaginal gel. The instructions are as follows:
- Lie down on your back.
- Insert the gel into the vagina.
- Lie down for 30 minutes.

Fig 24: This is a diagram showing how to use the vaginal suppository. The instructions are as follows:
- Lie down on your back.
- Insert the suppository into the vagina.
- Lie down for 30 minutes.

Fig 25: This is a diagram showing how to use the nasal inhaler. The instructions are as follows:
- Lie down on your back.
- Insert the inhaler into the nostril.
- Breathe in deeply.
- Lie down for 30 minutes.

Fig 26: This is a diagram showing how to use the nasal spray. The instructions are as follows:
- Lie down on your back.
- Insert the spray into the nostril.
- Breathe in deeply.
- Lie down for 30 minutes.

Fig 27: This is a diagram showing how to use the nasal drops. The instructions are as follows:
- Lie down on your back.
- Insert the drops into the nostril.
- Breathe in deeply.
- Lie down for 30 minutes.

Fig 28: This is a diagram showing how to use the nasal strips. The instructions are as follows:
- Lay the strips on the nose.
- Place them in position.
- Lie down for 30 minutes.

Fig 29: This is a diagram showing how to use the nasal paste. The instructions are as follows:
- Lay the paste on the nose.
- Place it in position.
- Lie down for 30 minutes.

Fig 30: This is a diagram showing how to use the nasal spray. The instructions are as follows:
- Lie down on your back.
- Insert the spray into the nostril.
- Breathe in deeply.
- Lie down for 30 minutes.

Fig 31: This is a diagram showing how to use the nasal drops. The instructions are as follows:
- Lie down on your back.
- Insert the drops into the nostril.
- Breathe in deeply.
- Lie down for 30 minutes.

Fig 32: This is a diagram showing how to use the nasal strips. The instructions are as follows:
- Lay the strips on the nose.
- Place them in position.
- Lie down for 30 minutes.

Fig 33: This is a diagram showing how to use the nasal paste. The instructions are as follows:
- Lay the paste on the nose.
- Place it in position.
- Lie down for 30 minutes.

Fig 34: This is a diagram showing how to use the nasal spray. The instructions are as follows:
- Lie down on your back.
- Insert the spray into the nostril.
- Breathe in deeply.
- Lie down for 30 minutes.

Fig 35: This is a diagram showing how to use the nasal drops. The instructions are as follows:
- Lie down on your back.
- Insert the drops into the nostril.
- Breathe in deeply.
- Lie down for 30 minutes.

Fig 36: This is a diagram showing how to use the nasal strips. The instructions are as follows:
- Lay the strips on the nose.
- Place them in position.
- Lie down for 30 minutes.

Fig 37: This is a diagram showing how to use the nasal paste. The instructions are as follows:
- Lay the paste on the nose.
- Place it in position.
- Lie down for 30 minutes.

Fig 38: This is a diagram showing how to use the nasal spray. The instructions are as follows:
- Lie down on your back.
- Insert the spray into the nostril.
- Breathe in deeply.
- Lie down for 30 minutes.

Fig 39: This is a diagram showing how to use the nasal drops. The instructions are as follows:
- Lie down on your back.
- Insert the drops into the nostril.
- Breathe in deeply.
- Lie down for 30 minutes.

Fig 40: This is a diagram showing how to use the nasal strips. The instructions are as follows:
- Lay the strips on the nose.
- Place them in position.
- Lie down for 30 minutes.

Fig 41: This is a diagram showing how to use the nasal paste. The instructions are as follows:
- Lay the paste on the nose.
- Place it in position.
- Lie down for 30 minutes.
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: 1mg (0.5ml) twice a day
  - Day 2: 3mg (1.5ml) twice a day
  - Day 3: 4mg (2ml) twice a day

  - 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 increased depending on your needs but will usually be between 4mg (2ml) and 8mg (4ml) a day.

For elderly patients or for those with liver/kidney disease:

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

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:

- Do not take a double dose.

If you stop taking Risperidone Oral Solution:

- Do not stop taking the solution 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 shaky movements.

4. POSSIBLE SIDE EFFECTS

- All medicines, Risperidone Oral Solution can cause side effects, although not everybody gets them. Many of these side effects get worse, 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 10 people) include:
  - dizziness
  - aggression or anxiety
  - headache
  - side effects that are less common (affecting up to one person in every 100 people) include:
  - dryness
  - drowsiness
  - difficulty in concentrating
  - sleep disorder
  - palpitations
  - indigestion
  - feeling or being sick (nausea or vomiting)
  - stomach ache
  - visual disturbances
  - weight gain
  - tiredness
  - local skin reactions or other allergic reactions such as itching, swelling, rashes or shortness of breath

- Side effects that are rare (affecting more than one person in 10,000 people) include:
  - breast swelling
  - fluid retention
  - weight gain
  - tiredness
  - skin problems
  - local skin reactions or other allergic reactions such as itching, swelling, rashes or shortness of breath

- Side effects that are very rare (affecting less than one person in 10,000 people) include:
  - excessive thirst or urination

5. HOW TO STORE Risperidone Oral Solution

- Keep out of the reach of children.

- This medicinal product does not require any special storage conditions.

- Do not refrigerate 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 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 milliliter (ml).
  - The solution also contains:
    - Water for injection, sodium hydrogen sulphate, sodium metabisulphite, sodium citrate dibasic and sodium hydroxide.

- What Risperidone Oral Solution looks like and contains 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 - PL Information

- To assist us in providing the best possible service, please could you answer the following questions:

- Please be ready to give the following information:

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Reference Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone Oral Solution</td>
<td>GB001111000</td>
</tr>
</tbody>
</table>

- The leaflet is last approved in July 2008.
1 ml of solution contains 1 mg of risperidone. Also contains sodium metabisulphite (E223). 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 bottle and the carton. 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.

Lock bottom type carton
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.

Opened on
PL 29831/0349 PA 1339/14/7

Risperidone 1mg/ml Oral Solution
For oral use

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-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors and, with lower affinity, to H1-histaminergic and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical 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

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

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)

<table>
<thead>
<tr>
<th>Parameters (unit)</th>
<th>Geometric Least Squares Mean</th>
<th>N = 12</th>
<th>% Ratio (A/B)</th>
<th>90% Confidence Interval</th>
<th>Intra CV (%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>Test (A) 9.2715</td>
<td>Reference (B) 9.6929</td>
<td>95.65 %</td>
<td>84.79 % - 107.91 %</td>
<td>16.40 %</td>
<td>85.70 %</td>
</tr>
<tr>
<td>AUC_{0-24} (ng·hr/mL)</td>
<td>Test (A) 60.7239</td>
<td>Reference (B) 63.2291</td>
<td>96.04 %</td>
<td>85.68 % - 107.64 %</td>
<td>15.51 %</td>
<td>89.13 %</td>
</tr>
<tr>
<td>AUC_{0-24} (ng·hr/mL)</td>
<td>Test (A) 62.6491</td>
<td>Reference (B) 65.0298</td>
<td>96.34 %</td>
<td>86.27 % - 107.58 %</td>
<td>15.00 %</td>
<td>90.94 %</td>
</tr>
</tbody>
</table>

**Figure No. 1a: Mean Plasma Concentration Time Curve for Risperidone**
Bioequivalence was confirmed for the parent. Intra-individual variability was markedly higher for the metabolite and as a consequence 90% CIs for $\text{C}_{\text{max}}$ 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 $\text{C}_{\text{max}}$ 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

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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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, dysopiramid, 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 \( \geq 10\% \)) 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 \(( \geq 1/10 \)) , common \(( \geq 1/100 \text{ to } <1/10 \)) , uncommon \(( \geq 1/1000 \text{ to } <1/100 \)) , rare \(( \geq 1/10,000 \text{ to } <1/1000 \)) , 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

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Blood prolactin increased, weight increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>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</td>
</tr>
<tr>
<td>Rare</td>
<td>Body temperature decreased</td>
</tr>
</tbody>
</table>

#### Cardiac disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Atrioventricular block, bundle branch block, atrial fibrillation, sinus bradycardia, palpitations</td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>

#### Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Anaemia, thrombocytopenia</td>
</tr>
<tr>
<td>Rare</td>
<td>Granulocytopenia</td>
</tr>
<tr>
<td>Not known</td>
<td>Agranulocytosis</td>
</tr>
</tbody>
</table>

#### Nervous system disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Parkinsonism, headache</td>
</tr>
<tr>
<td>Common</td>
<td>Akathisia, dizziness, tremor, dystonia, somnolence, sedation, lethargy, dyskinesia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Unresponsive to stimuli, loss of consciousness, syncope, depressed level of consciousness, cerebrovascular accident, transient ischaemic attack, dysarthria, disturbance in attention, hyperpyrexia, dizziness postural, balance disorder, tardive dyskinesia, speech disorder, coordination abnormal, hypoesthesia</td>
</tr>
<tr>
<td>Rare</td>
<td>Neuroleptic malignant syndrome, diabetic coma, cerebrovascular disorder, cerebral ischaemia, movement disorder</td>
</tr>
</tbody>
</table>

#### Eye disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vision blurred</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Conjunctivitis, ocular hyperaemia, eye discharge, eye swelling, dry eye, lacrimation increased, photophobia</td>
</tr>
<tr>
<td>Rare</td>
<td>Visual acuity reduced, eye rolling, glaucoma</td>
</tr>
</tbody>
</table>

#### Ear and labyrinth disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Ear pain, tinnitus</td>
</tr>
</tbody>
</table>

#### Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Dyspnoea, epistaxis, cough, nasal congestion, pharyngolaryngeal pain</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Wheezing, pneumonia aspiration, pulmonary congestion, respiratory disorder, rales, respiratory tract congestion, dysphonia</td>
</tr>
<tr>
<td>Rare</td>
<td>Sleep apnea syndrome, hyperventilation</td>
</tr>
</tbody>
</table>

#### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vomiting, diarrhoea, constipation, nausea, abdominal pain, dyspepsia, dry mouth, stomach discomfort</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dysphagia, gastritis, faecal incontinence, faecaloma</td>
</tr>
<tr>
<td>Rare</td>
<td>Intestinal obstruction, pancreatitis, lip swelling, cheilitis</td>
</tr>
</tbody>
</table>

#### Renal and urinary disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Enuresis</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dysuria, urinary incontinence, pollakiuria</td>
</tr>
</tbody>
</table>

#### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Rash, erythema</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Angioedema, skin lesion, skin disorder, pruritus, acne, skin discolouration, alopecia, seborrhoeic dermatitis, dry skin, hyperkeratosis</td>
</tr>
<tr>
<td>Rare</td>
<td>Dandruff</td>
</tr>
</tbody>
</table>

#### Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Arthralgia, back pain, pain in extremity</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Muscular weakness, myalgia, neck pain, joint swelling, posture abnormal, joint stiffness, musculoskeletal chest pain</td>
</tr>
</tbody>
</table>
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, acrodermatitis, 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 Amenorrhea, 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

— Hyperprolactinaemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhea, galactorrhea.

— 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 serotoninergic 5-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors and, with lower affinity, to H1-histaminergic and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, 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 Rating Scale (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 alpha1-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 isozenmes, 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 D2-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 D2 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.
PAR Risperidone 1mg/ml Oral Solution

UK/H/1174/001/DC

PACKAGE LEAFLET INFORMATION FOR THE USER
Risperidone

Before you start taking Risperidone

1. What Risperidone Oral Solution is and what it is for
Risperidone Oral Solution is used to treat the following:
- delusions and hallucinations in schizophrenia
- moderate to severe (grade 2) depression in adults

2. Before you take Risperidone Oral Solution
Check with your doctor or pharmacist before taking Risperidone Oral Solution if you:
- are allergic to any of the active substances or any of the other ingredients of Risperidone Oral Solution (see ‘Further information’ section).
- have a breast problem (e.g. breast lump) or any other conditions affecting the flow of breast milk.
- are pregnant or planning to become pregnant. Risperidone Oral Solution may cause breast changes in the male partner (see ‘Further information’ section).
- have a medical condition affecting the heart, lungs, liver, kidneys, eyes, or skin or have had a liver or kidney transplant.
- have a medical condition requiring medication changes or adjustments.
- have problems controlling your body temperature or sweating.
- have an uncontrolled high blood pressure or cannot tolerate these circumstances.
- have a history of serious adverse reactions to this medicine.
- have been told by your doctor to stop taking medicines for mood disorders or depression.
- have been told to stop taking medicines for mood disorders or depression.

3. How to take Risperidone Oral Solution

Dosage and method of administration

Risperidone Oral Solution is usually administered once or twice daily by mouth or by nasogastric tube. The dose may be increased or decreased as necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

Underlying conditions

Risperidone Oral Solution is usually administered once or twice daily by mouth or by nasogastric tube. The dose may be increased or decreased as necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

Mood disorders

Risperidone Oral Solution is usually administered once or twice daily by mouth or by nasogastric tube. The dose may be increased or decreased as necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

Driving and using machines

Risperidone Oral Solution is usually administered once or twice daily by mouth or by nasogastric tube. The dose may be increased or decreased as necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

Adverse effects

Risperidone Oral Solution is usually administered once or twice daily by mouth or by nasogastric tube. The dose may be increased or decreased as necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

Overdose

Risperidone Oral Solution is usually administered once or twice daily by mouth or by nasogastric tube. The dose may be increased or decreased as necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

Further information

Risperidone Oral Solution is usually administered once or twice daily by mouth or by nasogastric tube. The dose may be increased or decreased as necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

4. How much to take

For schizophrenia

Adults

The usual starting dose is 2mg per day, which may be increased to 4mg per day on the second day. The dose may be increased by 2mg per day on the third day, if necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

Children and adolescents

The usual starting dose is 0.5mg per day for children and 1mg per day for adolescents. The dose may be increased by 0.5mg per day on the second day, if necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

For the treatment of mood disorders

Adults

The usual starting dose is 2mg per day, which may be increased to 4mg per day on the second day. The dose may be increased by 2mg per day on the third day, if necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

Children and adolescents

The usual starting dose is 0.5mg per day for children and 1mg per day for adolescents. The dose may be increased by 0.5mg per day on the second day, if necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

For the treatment of bipolar disorder

Adults

The usual starting dose is 2mg per day, which may be increased to 4mg per day on the second day. The dose may be increased by 2mg per day on the third day, if necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

Children and adolescents

The usual starting dose is 0.5mg per day for children and 1mg per day for adolescents. The dose may be increased by 0.5mg per day on the second day, if necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

5. How to take Risperidone Oral Solution

Dosage and method of administration

Risperidone Oral Solution is usually administered once or twice daily by mouth or by nasogastric tube. The dose may be increased or decreased as necessary. The dose should be adjusted according to the response of the patient and the nature of the condition being treated.

Underlying conditions

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- THREATENING COMPLICATIONS OF UNCONTROLLED DIABETES

- THREATENING COMPLICATIONS OF UNCONTROLLED GLUCOSE METABOLISM

- THREATENING COMPLICATIONS OF UNCONTROLLED GLOLOMERIC FUNCTION

- THREATENING COMPLICATIONS OF UNCONTROLLED EYESIGHT

- THREATENING COMPLICATIONS OF UNCONTROLLED HEARIN