Public Assessment Report

Decentralised Procedure

Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-Coated Tablets

Risperidone

UK/H/1151/01-06/DC

UK licence no: PL 29831/0343-48

Applicant: Wockhardt UK Limited

LAY SUMMARY

The MHRA granted Wockhardt UK Limited Marketing Authorisations (licences) for the medicinal products Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg Film-Coated Tablets (PL 29831/0343-8) on 17th September 2008. These are prescription-only medicines (POM)

These are Decentralised applications for Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg Film-Coated Tablets submitted under Article 10.1 of Directive 2001/83.

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speak and behave The symptoms of these illnesses include delusions, hallucinations, unusual suspiciousness and becoming withdrawn.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 these applications and it was therefore judged that the benefits of taking Risperidone Film-Coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1

Product Name	Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg Film-Coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Risperidone
Form	Film-Coated Tablets
Strength	0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg Film-Coated Tablets
MA Holder	Wockhardt UK Limited
RMS	UK
CMS	IE
Procedure Number	UK/H/1151/01-06/DC
Timetable	Day 150– 30th July 2008

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 0.5mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.5mg of risperidone.

Excipients:
Lactose monohydrate – 78.05mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Brown, capsule-shaped tablets with breakline on one side and plain on the other side. The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

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

4.2 Posology and method of administration

4.2. 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 Tablets 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.

4.2. 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 Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

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

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

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAE)

Risperidone Tablets are 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

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

4.6 Pregnancy and lactation

Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats. No teratogenic effect of risperidone was noted in any study. The

safety of risperidone for use during human pregnancy has not been established. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. Therefore, risperidone should only be used during pregnancy if the benefits outweigh the risks.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

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

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

4.9 Overdose

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension,

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacokinetic properties

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

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

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

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

Sodium laurilsulfate
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Hypromellose
Colloidal anhydrous silica
Magnesium stearate

Coating (Opadry 04H86736):
Hypromellose 6 cP
Titanium dioxide (E171)
Talc

Propylene glycol (E1520)
Iron oxide red (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
The tablets are packed in PVC/PVdC blister strips consisting of 200µm polyvinyl chloride/25µm low density polyethylene/polyvinylidene chloride and 20µm aluminium foil.

The strips are packed in a cardboard carton containing 20 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham,
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0343

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/09/2008

10 DATE OF REVISION OF THE TEXT
17/09/2008

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 1mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1mg of risperidone.

Excipients:
Lactose monohydrate – 156.1mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, capsule-shaped tablets with breakline on one side and plain on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

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

4.2 Posology and method of administration

4.2. 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 Tablets 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.

4.2. 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 Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

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

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

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAE)

Risperidone Tablets are 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

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

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

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

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

4.9 Overdose

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a

laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacokinetic properties

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

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

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

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

Sodium laurilsulfate
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Hypromellose
Colloidal anhydrous silica
Magnesium stearate

Coating (Opadry 04H59030):
Hypromellose 15cP
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
The tablets are packed in PVC/PVdC blister strips consisting of 200µm polyvinyl chloride/25µm low density polyethylene/polyvinylidene chloride and 20µm aluminium foil.

The strips are packed in a cardboard carton containing 20 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham,
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0344

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/09/2008

10 DATE OF REVISION OF THE TEXT
17/09/2008

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 2mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2mg of risperidone.

Excipients:
Lactose monohydrate – 155.1mg
Sunset yellow FCF (E110)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Orange, capsule-shaped tablets with breakline on one side and plain on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

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

4.2 Posology and method of administration

4.2. 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 Tablets 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.

4.2. 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 Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

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

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

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAE)

Risperidone Tablets are 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sunset yellow FCF (E110) may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

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

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

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

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

4.9 Overdose

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should be considered.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacokinetic properties

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

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

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

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

Sodium laurilsulfate
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Hypromellose
Colloidal anhydrous silica
Magnesium stearate

Coating (Opadry 04H53765):
Titanium dioxide (E171)
Hypromellose 15cP
Talc
Propylene glycol (E1520)
Sunset yellow FCF (E110)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
The tablets are packed in PVC/PVdC blister strips consisting of 200µm polyvinyl chloride/25µm low density polyethylene/polyvinylidene chloride and 20µm aluminium foil.

The strips are packed in a cardboard carton containing 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham,
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0345

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/09/2008

10 DATE OF REVISION OF THE TEXT
17/09/2008

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 3mg Fim-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 3mg of risperidone.

Excipients:
Lactose monohydrate - 232.65mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, capsule-shaped tablets with breakline on one side and plain on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

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

4.2 Posology and method of administration

4.2. 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 Tablets 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.

4.2. 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 Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

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

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

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAE)

Risperidone Tablets are 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

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

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

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

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

4.9 Overdose

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a

laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacokinetic properties

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

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

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

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

Sodium laurilsulfate
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Hypromellose
Colloidal anhydrous silica
Magnesium stearate

Coating (Opadry 04H82861):
Hypromellose
Quinoline yellow (E104)
Titanium dioxide (E171)
Talc
Propylene glycol (E1520)
Yellow iron oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
The tablets are packed in PVC/PVdC blister strips consisting of 200µm polyvinyl chloride/25µm low density polyethylene/polyvinylidene chloride and 20µm aluminium foil.

The strips are packed in a cardboard carton containing 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham,
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0346

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT
17/09/2008

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 4mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 4mg of risperidone.

Excipients:
Lactose monohydrate - 310.2mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Green, capsule-shaped tablets with breakline on one side and plain on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

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

4.2 Posology and method of administration

4.2. 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 Tablets 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.

4.2. 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 Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

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

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

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAE)

Risperidone Tablets are 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

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

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

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

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

4.9 Overdose

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a

laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacokinetic properties

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

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

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

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

Sodium laurilsulfate
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Hypromellose
Colloidal anhydrous silica
Magnesium stearate

Coating (Opadry 04H51499):
Hypromellose
Quinoline yellow (E104)
Titanium dioxide (E171)
Talc
Propylene glycol (E1520)
Indigo carmine (E132)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
The tablets are packed in PVC/PVdC blister strips consisting of 200µm polyvinyl chloride/25µm low density polyethylene/polyvinylidene chloride and 20µm aluminium foil.

The strips are packed in a cardboard carton containing 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham,
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0347

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/09/2008

10 DATE OF REVISION OF THE TEXT
17/09/2008

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 6mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 6mg of risperidone.

Excipients:
Lactose monohydrate – 135.39mg
Sunset yellow FCF (E110)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Orange, round tablets, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

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

4.2 Posology and method of administration

4.2. 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 Tablets 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.

4.2. 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 Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

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

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

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAE)

Risperidone Tablets are 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sunset yellow FCF (E110) may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

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

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

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

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

4.9 Overdose

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a

laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacokinetic properties

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

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

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

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

Sodium laurilsulfate
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Hypromellose
Colloidal anhydrous silica
Magnesium stearate

Coating (Opadry 03H53786):
Hypromellose
Titanium dioxide (E171)
Talc
Quinoline yellow (E104)
Propylene glycol (E1520)
Sunset yellow FCF (E110)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
The tablets are packed in PVC/PVdC blister strips consisting of 200µm polyvinyl chloride/25µm low density polyethylene/polyvinylidene chloride and 20µm aluminium foil.

The strips are packed in a cardboard carton containing 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham,
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0348

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/09/2008

10 DATE OF REVISION OF THE TEXT
17/09/2008

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER
Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg film-coated Tablets
Risperidone

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

In this leaflet:

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

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

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

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

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

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

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

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

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

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

Risperidone Tablets can be taken with or without food.

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

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

Important information about some of the ingredients of Risperidone Tablets
If you have been told by your doctor that you have **intolerance to some sugars**, you should contact your doctor before taking Risperidone Tablets.

The 2mg and 6mg tablets contain sunset yellow FCF (E110) this may cause allergic reactions in some patients. Allergy is more common in those people who are allergic to aspirin.

3. HOW TO TAKE RISPERIDONE TABLETS
Always take Risperidone Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Risperidone Tablets can be taken with or without food. Swallow your tablets whole with a glass of water. Keep taking the tablets every day.

Your doctor will tell you how many Risperidone Tablets to take and for how long you should take them.

For adults and adolescents over 15 years of age with conditions which affect the way you think, feel, speak or behave:
The dose will be increased gradually over the first days of treatment as follows:
- Day 1 – 2mg
- Day 2 – 4mg

This will be taken as either a single dose or as half the dose in the morning and half the dose in the evening.

The dose will then be set depending on your needs but will usually be between 4mg and 6mg a day.

For adults and adolescents over 15 years of age with bipolar disorder:
A starting dose of 2mg once a day is recommended. This may be increased to 6mg per day depending on your requirements. Your doctor will tell you what dose is suitable for your situation.

For elderly patients or for those with liver or kidney disease
You should take half of the above doses. You will be told how many tablets to take.

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

104036/1

pg1/2

WOCKHARDT CREATIVE UNIT	CUSTOMER	PRODUCT
	CP PHARMA	Risperidone Tablets
SIZE (w)209 x (h)297mm	PHARMACODE No. 161	BARCODE No.
FILE NAME : Risperidone_Lit_104036-1.ai		ARTWORK (DETAILS) RECEIVED ON : 18th MARCH, 2008
SOFTWARE : ADOBE ILLUSTRATOR CS2		PROOF REVISION: ☑ 1st PDF sent on - 2ND APRIL 2008 ☑ 2nd PDF sent on - 5TH MAY 2008 ☑ 3rd PDF sent on - 15TH MAY 2008 ☑ 4th PDF sent on - 16TH JUNE 2008 ☑ 5th PDF sent on - 24TH JUNE 2008
TYPEFACES : MYRIAD PRO / BOLD		

PROCESS BLACK

If you stop taking Risperidone Tablets
Do not stop your treatment just because you feel better. It is important that you continue to take the tablets for as long as the doctor has told you.
You should always check with your doctor before you stop treatment. Your doctor may want to reduce gradually the amount you are taking, especially if you have been taking a high dose.This will help to prevent a recurrence of the original trouble and reduce the chance of withdrawal effects such as feeling sick, vomiting, sweating, sleeplessness, muscle stiffness or jerky movements.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Risperidone Tablets can cause side effects, although not everybody gets them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
Side effects that are common (affecting more than one person in every 10 people) include:
• difficulty in sleeping
• agitation or anxiety
• headache
Side effects that are less common (affecting up to nine people in every 100 people) include:
• sleepiness
• tiredness
• dizziness
• difficulty in concentrating
• blurred vision
• constipation
• indigestion
• feeling or being sick (nausea or vomiting)
• stomach ache
• sexual potency problems
• urinary incontinence (leakage of urine)
• runny or blocked nose
• liver problems
• local skin rash or swelling or other allergic reactions such as itching, swollen face or lips or shortness of breath
• weight gain or swelling of the ankles
Side effects that are rare (affecting up to nine people in 10 thousand people) include:
• breast swelling in men and women
• convulsions (fits)
Side effects that are very rare (affecting less than one person in 10 thousand people) include:
• excessive thirst or urination
If you experience any of the following, **stop taking Risperidone Tablets** and contact a doctor or the nearest hospital immediately:
• weakness or numbness of the face, arms or legs
• slurred speech
• trembling, muscle stiffness or spasm
• slowness of movement, excess saliva, restlessness or rolling of the eyes
• fever, fast breathing, sweating, muscle stiffness and reduced consciousness
• long lasting and painful erection
It is important to tell your doctor or pharmacist if you suffer from any of these or any other undesirable effects which are not listed above.

5. HOW TO STORE RISPERIDONE TABLETS
Keep out of the reach and sight of children.
Store the tablets below 30°C. Store in the original package.
Do not use Risperidone Tablets after the expiry date which is stated on the blister and the carton. The expiry date refers to the last day of the month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Risperidone Tablets contain
The active substance is risperidone. Each tablet contains 0.5mg, 1mg, 2mg, 3mg, 4mg or 6mg risperidone.
Other ingredients are sodium laurilsulphate, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal anhydrous silica, hypromellose and magnesium stearate.
The tablets also contain:
0.5mg: hypromellose 6 cP, titanium dioxide (E171), talc, propylene glycol(E1520) and iron oxide red (E172)
1mg: hypromellose 15 cP, propylene glycol (E1520)
2mg: titanium dioxide (E171), hypromellose 15 cP, propylene glycol (E1520), talc, sunset yellow FCF (E110)
3mg: hypromellose, quinoline yellow (E104), titanium dioxide (E171), propylene glycol (E1520), talc, yellow iron oxide (E172)
4mg: hypromellose, quinoline yellow (E104), propylene glycol (E1520), titanium dioxide (E171), talc, indigo carmine (E132)
6mg: hypromellose, titanium dioxide (E171), quinoline yellow (E104), propylene glycol (E1520), talc, sunset yellow FCF (E110)
What Risperidone Tablets look like and contents of the pack
0.5mg: brown, capsule-shaped, film-coated tablets with breakline on one side and plain on the other side - 20 tablet pack
1mg: white, capsule-shaped, film-coated tablets with breakline on one side and plain on the other side - 20 or 60 tablet pack
2mg: orange, capsule-shaped, film-coated tablets with breakline on one side and plain on the other side - 60 tablet pack
3mg: yellow, capsule-shaped, film-coated tablets with breakline on one side and plain on the other side - 60 tablet pack
4mg: green, capsule-shaped, film-coated tablets with breakline on one side and plain on the other side - 60 tablet pack
6mg: orange, round, film-coated tablets - 28 tablet pack
The 0.5mg, 1mg, 2mg, 3mg & 4mg tablets can be divided into equal halves.
Risperidone Tablets - PIL Information
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:
0800 198 5000 (UK Only)
Please be ready to give the following information:

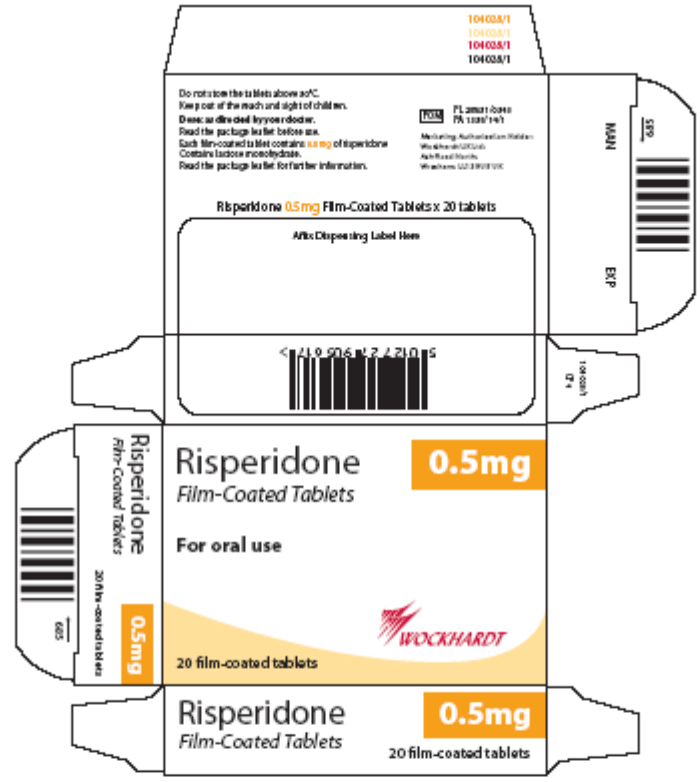
Product Name	Reference Number
Risperidone 0.5mg Film-Coated Tablets	29831/0343
Risperidone 1mg Film-Coated Tablets	29831/0344
Risperidone 2mg Film-Coated Tablets	29831/0345
Risperidone 3mg Film-Coated Tablets	29831/0346
Risperidone 4mg Film-Coated Tablets	29831/0347
Risperidone 6mg Film-Coated Tablets	29831/0348

This is a service provided by the Royal National Institute of Blind People.
For the Republic of Ireland please call + 353 52 36253.
Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK
Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.
This medicinal product is authorised in the Member States of the EEA under the following names:
Ireland – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg or 6mg Film-Coated Tablets
This leaflet was last approved in July 2008.

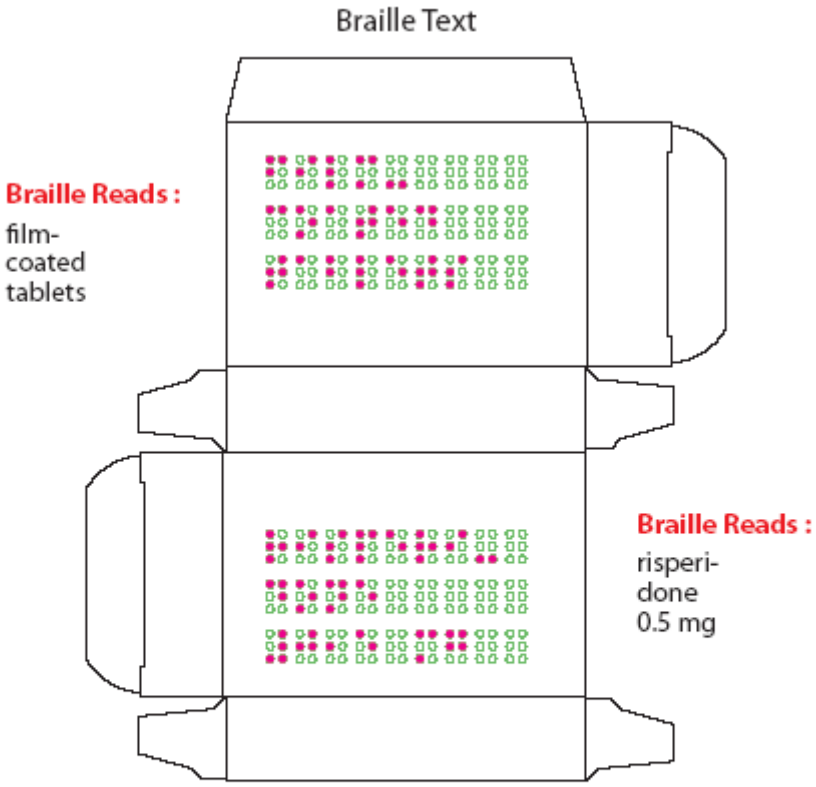
WOCKHARDT

CP4
104036/1

MODULE 4


Risperidone 0.5mg Film-Coated Tablets x 20 tablets
Affix Dispensing Label Here
Risperidone
Film-Coated Tablets
0.5mg
For oral use
WOCKHARDT
20 film-coated tablets
Risperidone
Film-Coated Tablets
0.5mg
20 film-coated tablets


WOCKHARDT
CREATIVE UNIT
CP PHARMA
PANTONE 199
PANTONE 130
PANTONE 134
PROCESS BLACK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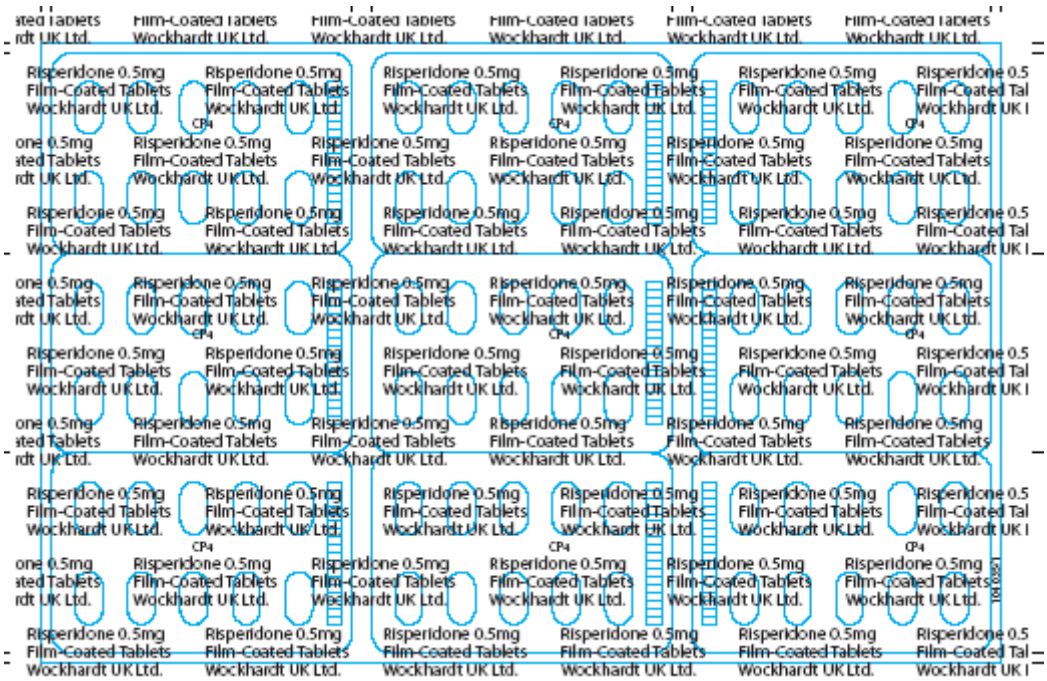
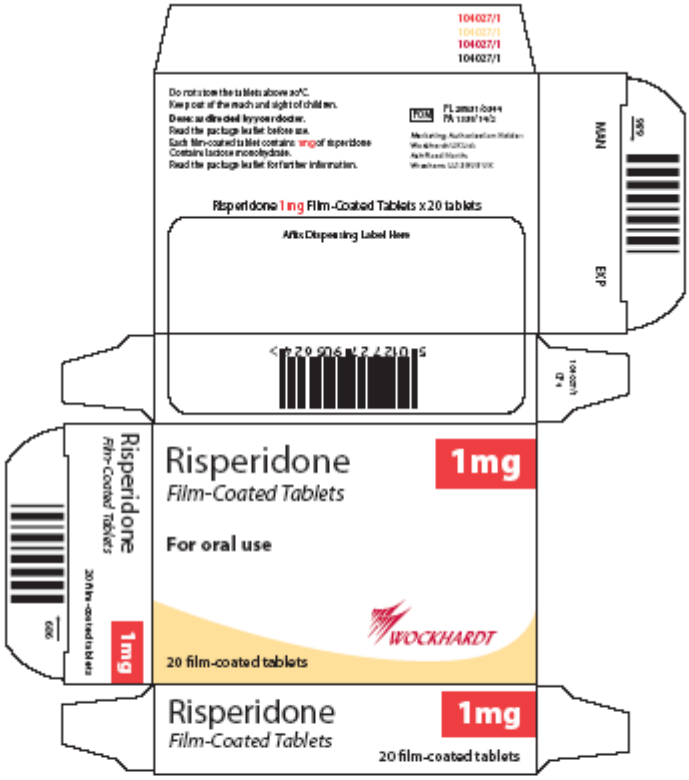
film-
coated
tablets
Braille Reads :
risperi-
done
0.5 mg


Risperidone 0.5mg
Film-Coated Tablets
Wockhardt UK Ltd.
CP4



WOCKHARDT CREATIVE UNIT	CUSTOMER: CP PHARMA	PRODUCT: Risperidone 1mg - 20 Tablets
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FILE NAME: Risperidone 20tab_1mg_Cds_104027-1.ai	ARTWORK (CDS/PLD) RECEIVED ON: 14th APRIL, 2006	
SOFTWARE: ADOBE ILLUSTRATOR CS2	PROOF REVISION: ☑ 1st PDF sent on - 18TH APRIL 2006 ☑ 2nd PDF sent on - 17TH APRIL 2006 ☑ 3rd PDF sent on - 21TH MAY 2006	
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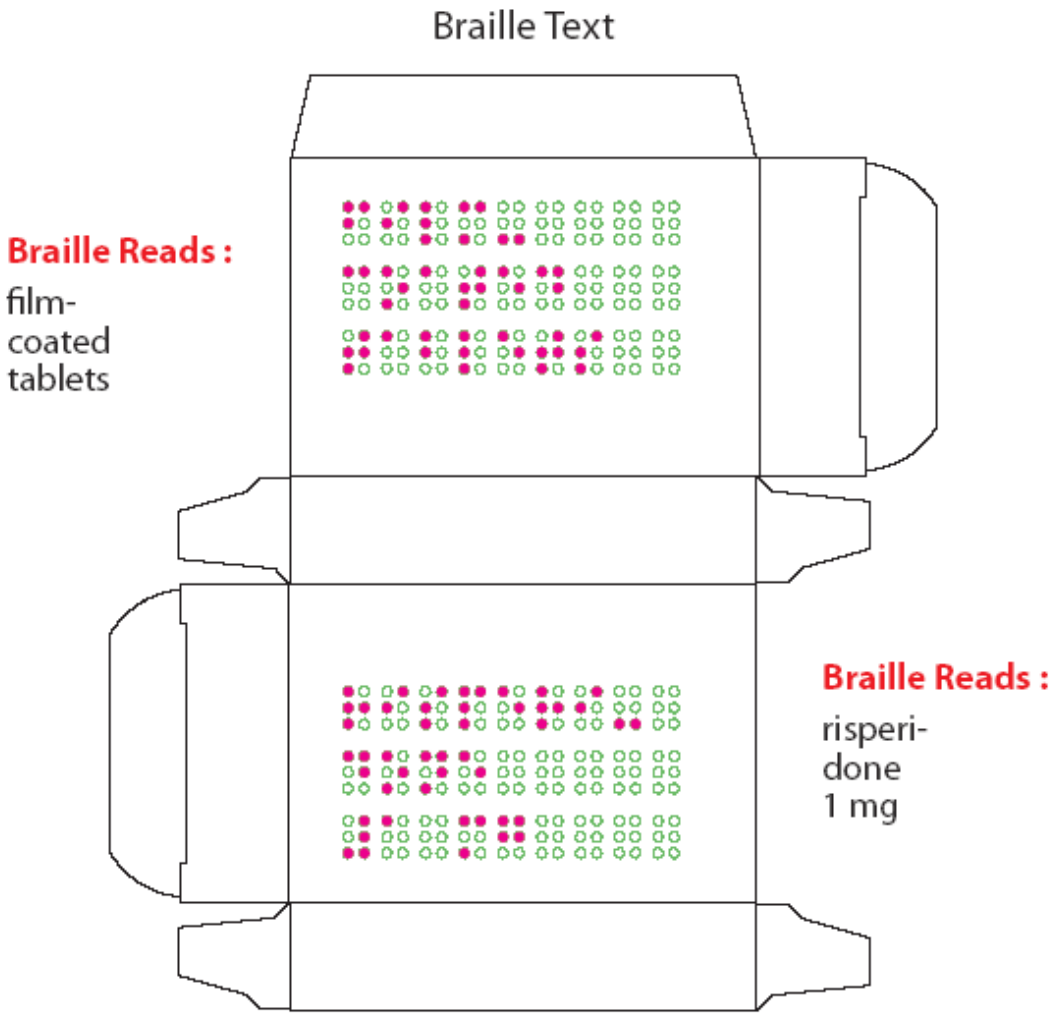
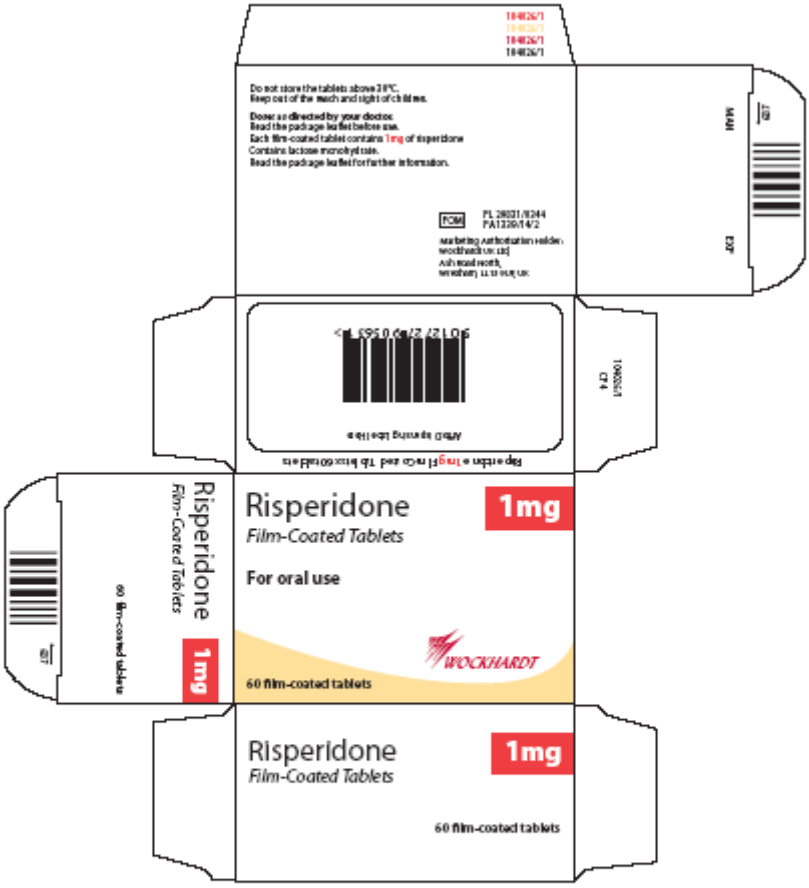

Braille Text
Braille Reads :
film-
coated
tablets
Braille Reads :
risperi-
done
1 mg


Do not store the tablets above 30°C.
Keep out of the reach and sight of children.
Dose as directed by your doctor.
Read the package leaflet before use.
Each film-coated tablet contains 1mg of risperidone
Contains lactose monohydrate.
Read the package leaflet for further information.
POM
PL 28031/0244
PA1329/14/2
Risperidone
Film-Coated Tablets
1mg
For oral use
WOCKHARDT
60 film-coated tablets
Risperidone
Film-Coated Tablets
1mg
60 film-coated tablets


WOCKHARDT
CREATIVE UNIT
CUSTOMER
CP PHARMA
PRODUCT
PANTONE 032
PANTONE 101
PANTONE 126
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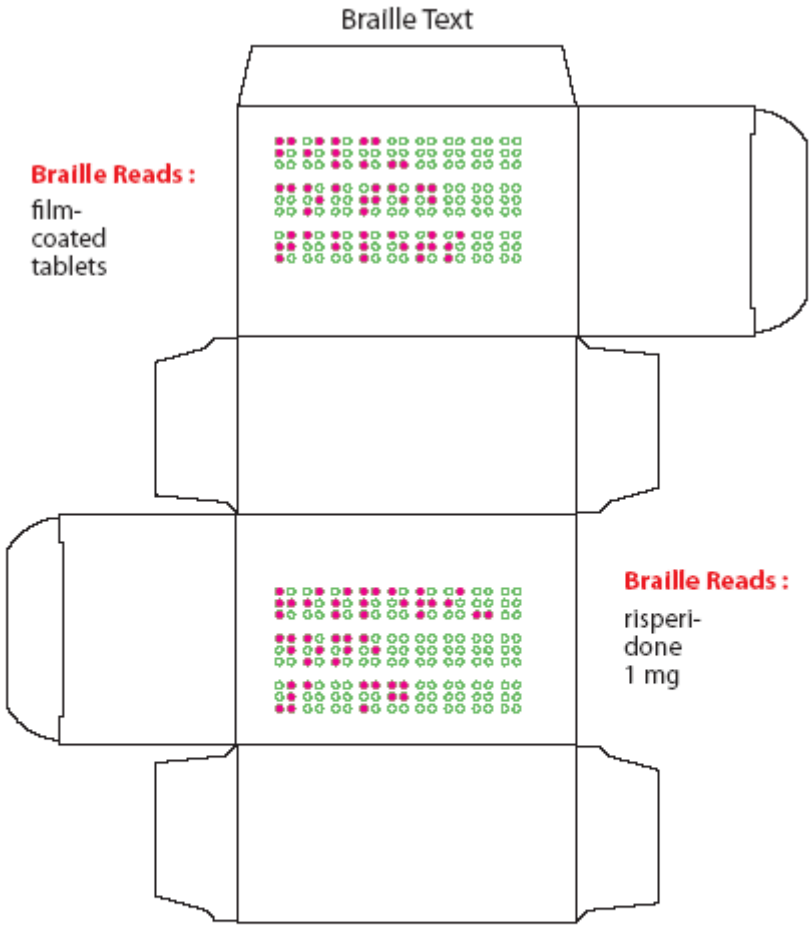
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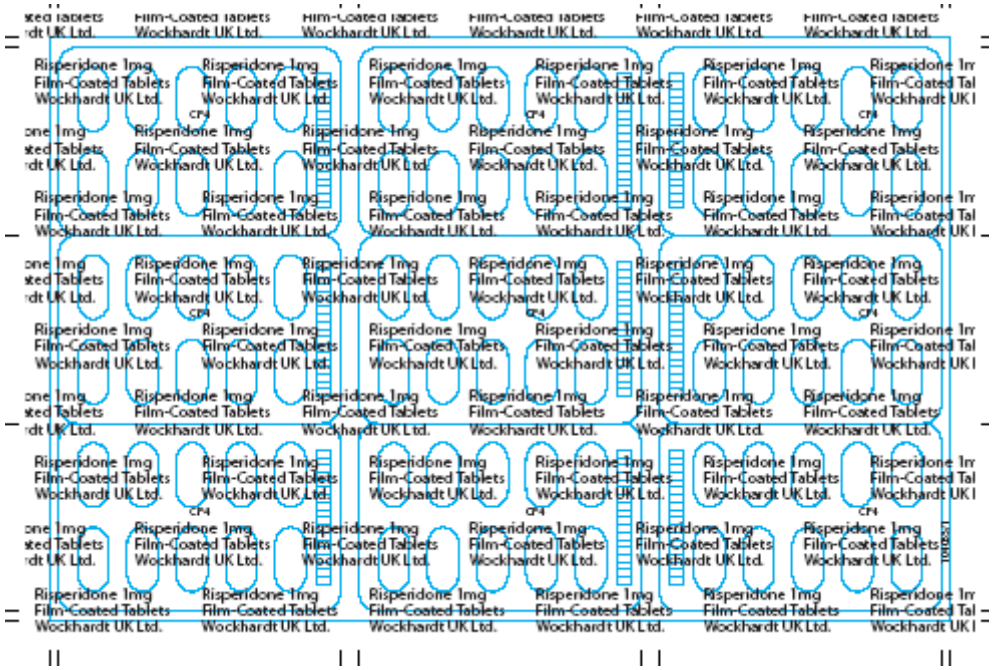
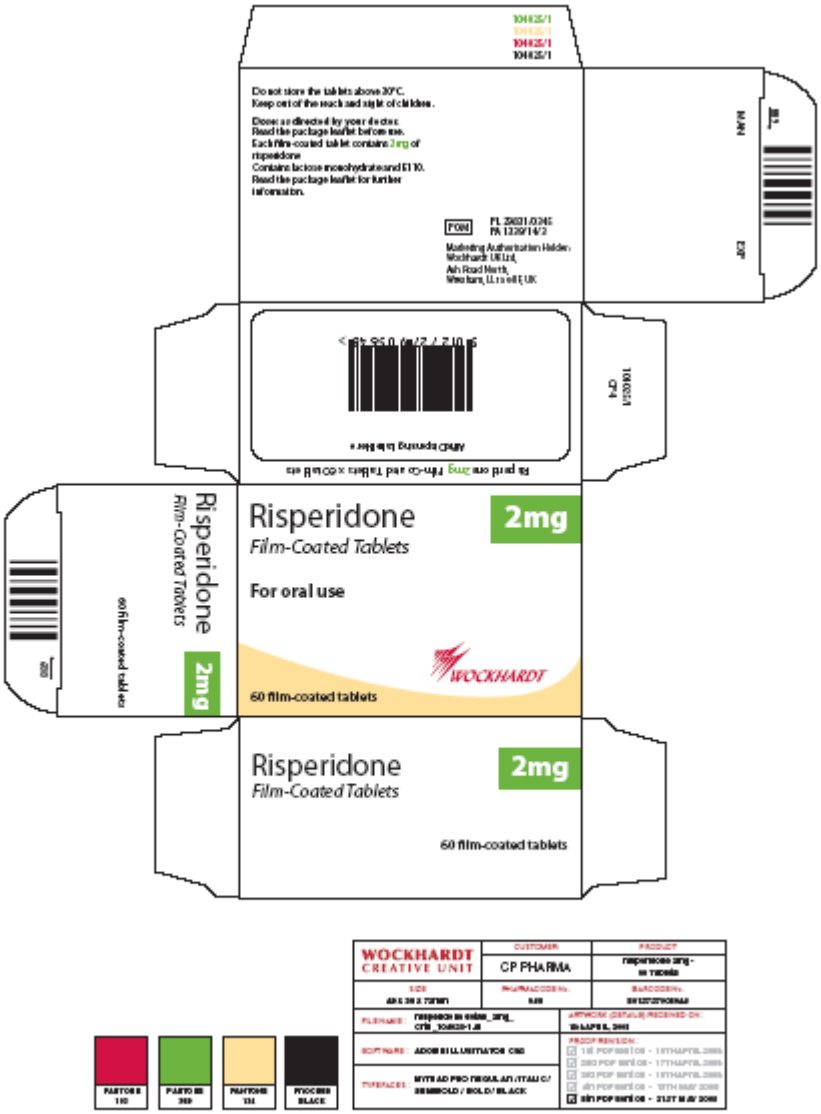
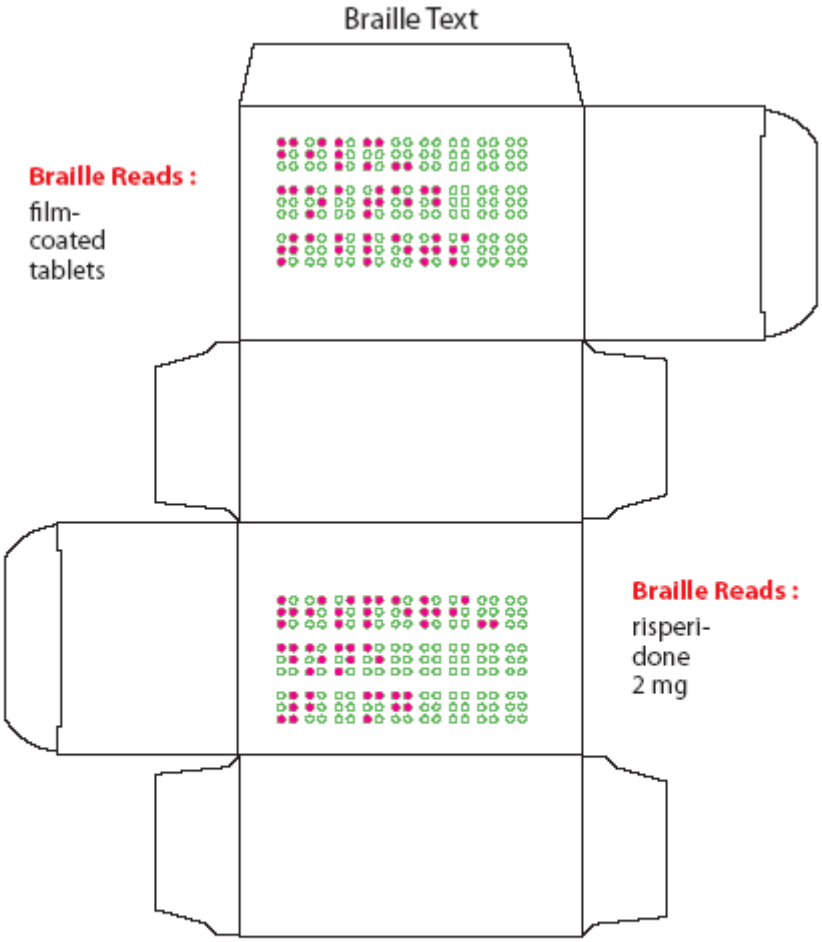
film-
coated
tablets
Braille Reads :
risperi-
done
1 mg


Risperidone 1mg
Film-Coated Tablets
Wockhardt UK Ltd.
CP4


Do not store the tablets above 30°C.
Keep out of the reach and sight of children.
Dose: as directed by your doctor.
Read the package leaflet before use.
Each film-coated tablet contains 2 mg of risperidone
Contains lactose monohydrate and E110.
Read the package leaflet for further information.
PL 20031/0245
PA 1329/14/2
Marketing Authorisation Holder:
Wockhardt UK Ltd,
Ash Road North,
Wrexham, LL13 9UF, UK
Risperidone
Film-Coated Tablets
2mg
For oral use
WOCKHARDT
60 film-coated tablets
Risperidone
Film-Coated Tablets
2mg
60 film-coated tablets
Risperidone
Film-Coated Tablets
2mg
60 film-coated tablets

WOCKHARDT
CREATIVE UNIT
CP PHARMA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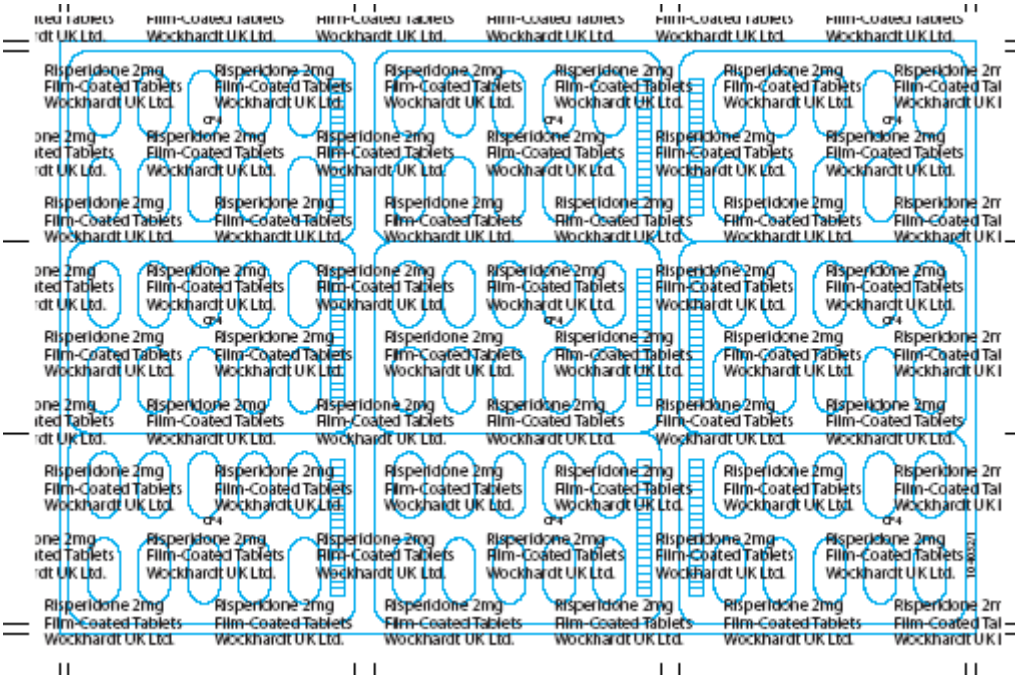
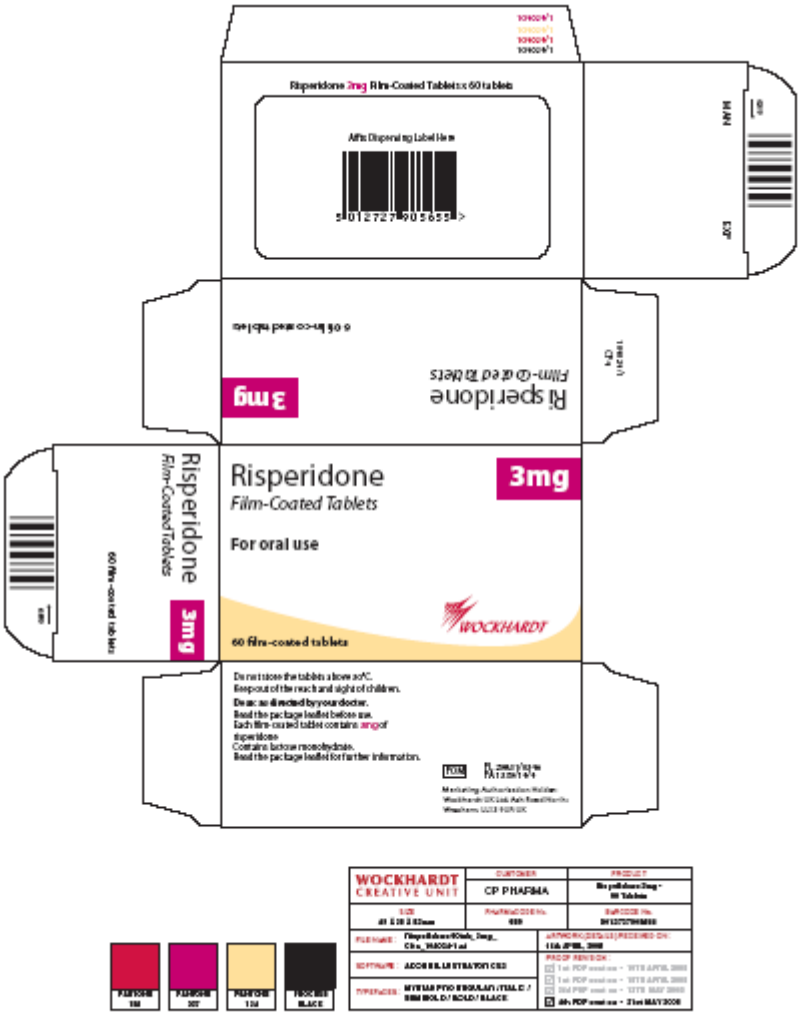
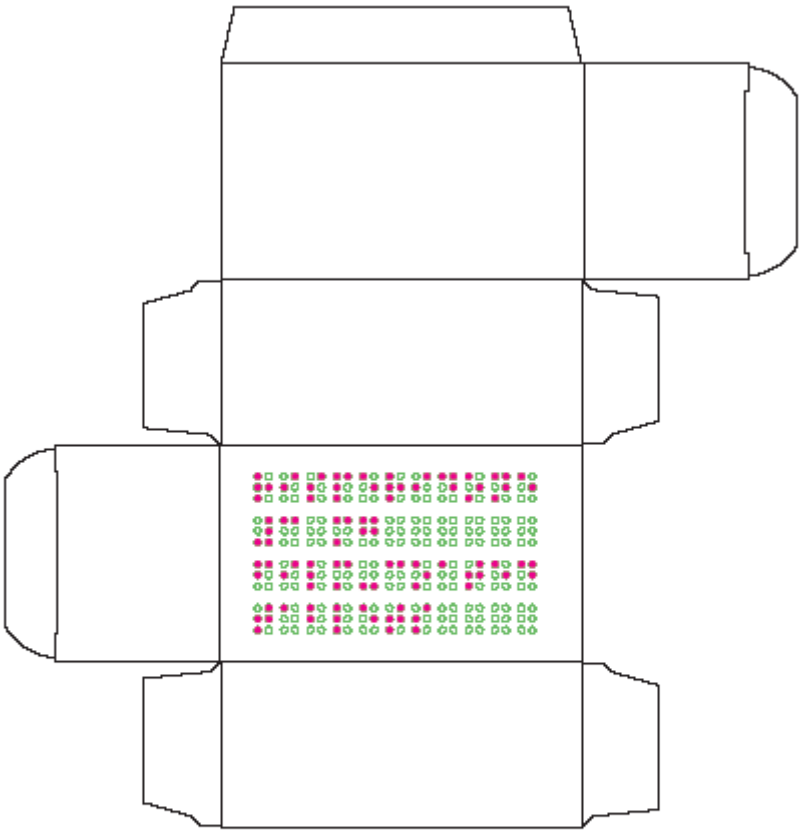
film-
coated
tablets
Braille Reads :
risperi-
done
2 mg


Risperidone 2mg
Film-Coated Tablets
Wockhardt UK Ltd.


Risperidone 3mg Film-Coated Tablets x 60 tablets
Affix Dispensing Label Here
5012727905655
Risperidone
Film-Coated Tablets
3mg
For oral use
60 film-coated tablets
WOCKHARDT
Do not store the tablets above 30°C.
Keep out of the reach and sight of children.
Do not use unless directed by your doctor.
Read the package leaflet before use.
Each film-coated tablet contains 3mg of risperidone.
Contains lactose monohydrate.
Read the package leaflet for further information.
POM
Marketing Authorisation Holder:
Wockhardt (UK) Ltd, Ash Road North,
Wrexham, LL13 9UF, UK

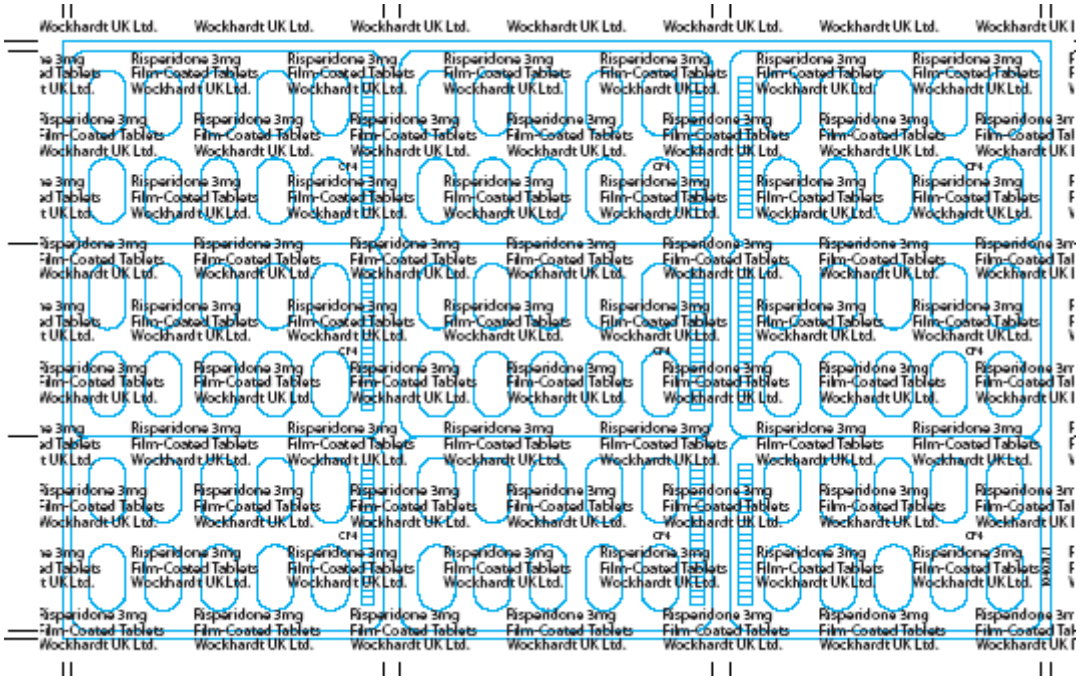
WOCKHARDT
CREATIVE UNIT
CUSTOMER
CP PHARMA
PRODUCT
Risperidone 3mg - 60 Tablets
SIZE
PHARMACODE No.
BarCODE No.
FILE NAME:
APPROVED DATE/SIGNED ON:
11th APRIL, 2008
SOFTWARE:
PROOF REVISION:
1st PDF created on - 10TH APRIL 2008
1st PDF created on - 10TH APRIL 2008
2nd PDF created on - 12TH MAY 2008
4th PDF created on - 21st MAY 2008
TYPEFACE(S):
MYRIAD PRO REGULAR / ITALIC / SEMIBOLD / BOLD / BLACK
PANTONE 186
PANTONE 207
PANTONE 124
PROCESS BLACK

Braille Text



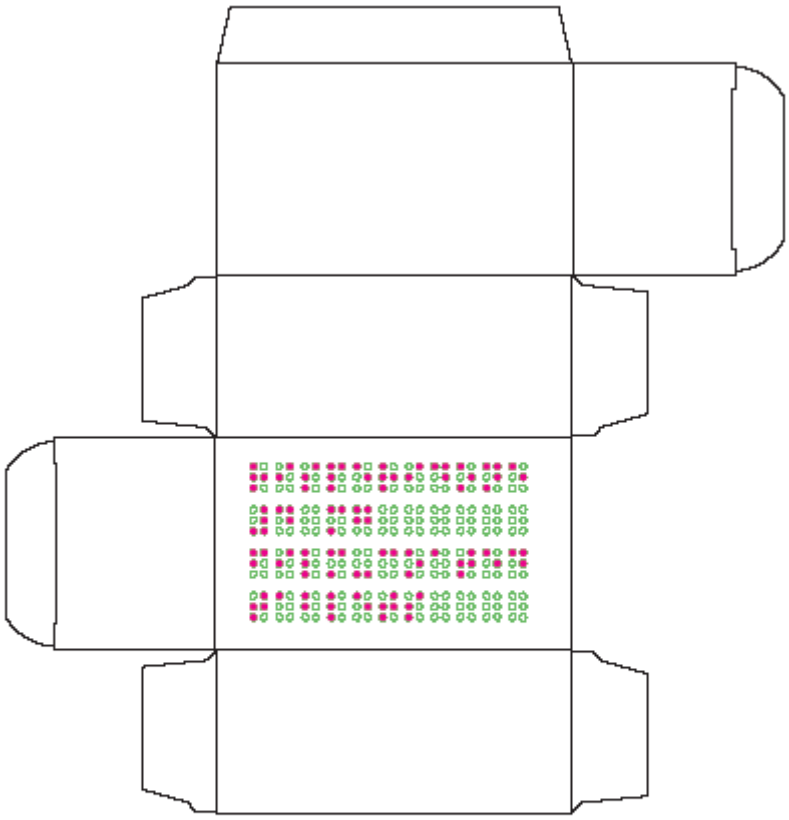
Braille Reads:

risperidone
3 mg
film-coated
tablets




Risperidone 4mg Film-Coated Tablets x 60 tablets
Alfa Dispensing Label Here
Risperidone
Film-Coated Tablets
4mg
For oral use
WOCKHARDT
60 film-coated tablets
Do not store the tablets above 30°C.
Keep out of the reach and sight of children.
Dose as directed by your doctor.
Read the package leaflet before use.
Each film-coated tablet contains 4mg of risperidone
Contains lactose monohydrate.
Read the package leaflet for further information.
POM
WOCKHARDT
CREATIVE UNIT
CIPPHARMA

Braille Text



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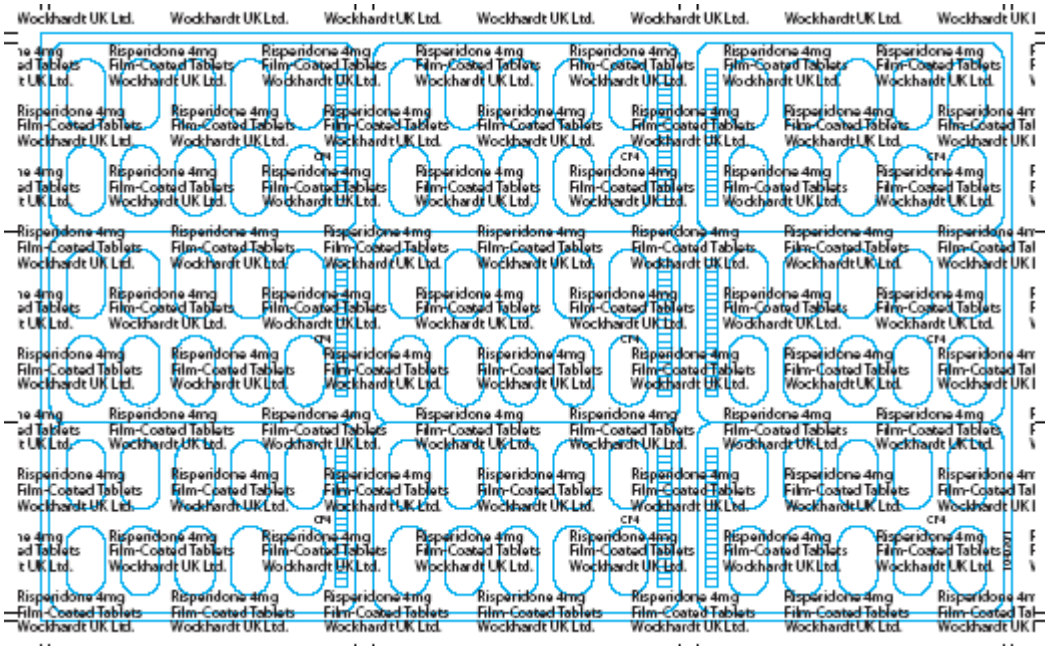
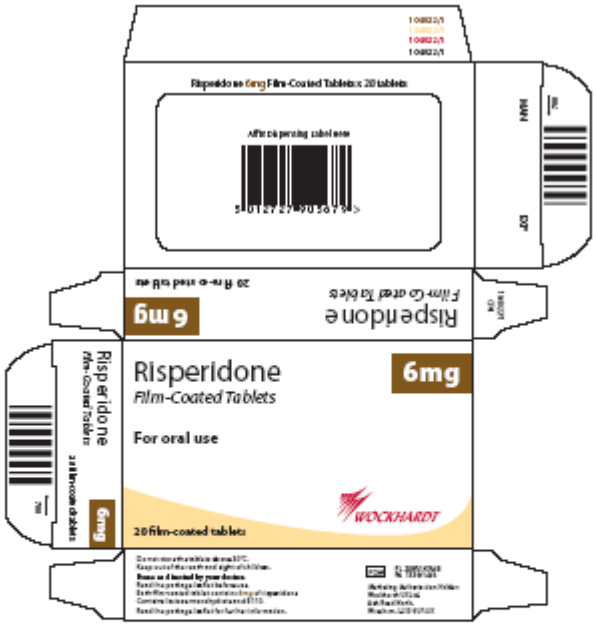
risperidone
4 mg
film-coated
tablets





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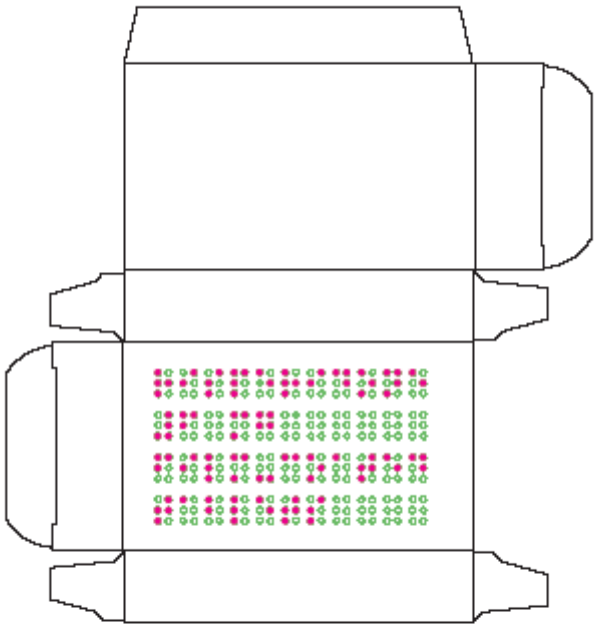
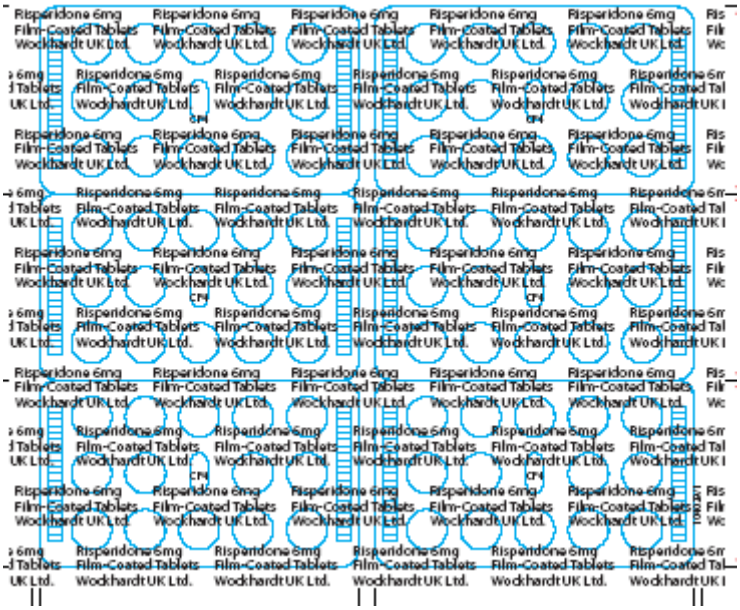


Braille Reads :

risperidone
6 mg
film-coated
tablets


Risperidone 6mg
Film-Coated Tablets
Wockhardt UK Ltd.

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 0.5mg/1mg/2mg/3mg/4mg/6mg Tablets, in the treatment of acute and chronic schizophrenic psychoses and for the treatment of mania in bipolar disorder, is approvable.

The application for Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg film-coated tablets are abridged applications 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 products refer to Janssen-Cilag Ltd Risperdal tablets (PL 00242/0347 – 0.5mg, PL 00242/0186 – 1mg, PL 00242/0187 – 2mg, PL 00242/0188 – 3mg, PL 00242/0189 – 4mg, PL 00242/0317 – 6mg) for the 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg strength applications respectively.

Risperidone has a well established clinical and toxicological profile. Risperdal is indicated for the treatment of acute and chronic schizophrenic psychoses, and for the treatment of mania in bipolar disorder.

No new preclinical studies were submitted with these applications. The applicant has submitted two single dose bioequivalence studies, one fed and one fasted.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Risperidone 0.5mg/1mg/2mg/3mg/4mg/6mg Film Coated Tablets
Name(s) of the active substance(s) (INN)	Risperidone
Pharmacotherapeutic classification (ATC code)	N05AX
Pharmaceutical form and strength(s)	Film-coated Tablets 0.5mg/1mg/2mg/3mg/4mg/6mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1151/01-06/DC
Reference Member State	United Kingdom
Member States Concerned	IE
Marketing Authorisation Number(s)	PL 29831/0343-8
Name and address of the authorisation holder	Wockhardt UK Limited, Ash Road, North Wrexham, LL13 9UF, UK

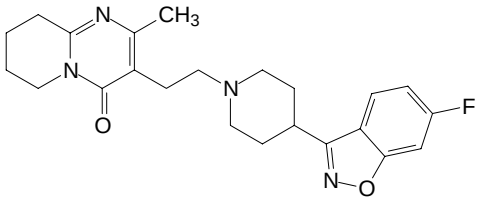
III SCIENTIFIC OVERVIEW AND DISCUSSION

DRUG SUBSTANCE

Nomenclature

rINN: Risperidone

Structure



Chemical Name; 3-{2-[4[(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one

Molecular Formula: $C_{23}H_{27}FN_4O_2$

Molecular Weight: 410.5

General Properties

Risperidone is a white to off-white powder, practically insoluble in water, freely soluble in methylene chloride, and sparingly soluble in alcohol. It dissolves in dilute acid solutions.

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.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely colloidal anhydrous silica, lactose monohydrate, sodium laurilsulfate, microcrystalline cellulose, hypromellose, sodium starch glycolate(type A), magnesium stearate, opadry 04H86736 Brown, Opadry 04H59030 Clear, Opadry 04H53765 Orange, Opadry 04H82861 Yellow, Opadry 04H51499 Green, Opadry 03H53786 Orange and water purified.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of OPADRY which comply with in-House specifications.

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

Dissolution and Impurity profiles

Dissolution and impurity profiles for all strengths of the drug product were found to be generic medicinal products equivalent to those of the reference products.

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 PVDC-coated, PVC, LDPE and aluminium blisters. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage condition ‘Do not store above 30 degree C’ is proposed 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 Authorisations are granted for these applications.

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 these applications and none are required for an application of this type.

CLINICAL ASPECTS

1. INTRODUCTION

These are outgoing Decentralised applications for six strengths of Risperidone Tablets (0.5, 1, 2, 3, 4 and 6 mg). These abridged standard applications are submitted under Article 10(1) of Directive 2001/83/EC. The applicants Risperidone tablets claim equivalence to Risperdal 1, 2, 3 and 4mg tablets (PL 00242/0186-0189) - first authorisation was granted to Janssen-Cilag Limited in the U.K. on 8th December 1992, followed by further authorisations on 15th July 1997 (6mg – PL 00242/0317) and 30th June 2000 (0.25 and 0.5mg – PL 00242/0346 and 0347).

2. BACKGROUND

Risperidone is well characterised in the literature and is indicated for the treatment of acute and chronic schizophrenic psychoses. It belongs to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2 receptors. It binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. It has no affinity for cholinergic receptors. Although Risperidone is a potent D_2 antagonist, which is considered to be the principal mechanism by which it improves 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.

3. INDICATIONS

Risperidone Tablets are 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 Tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone Tablets are 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 Tablets are not licensed for the treatment of behavioural symptoms of dementia

4. DOSE & DOSE SCHEDULE

4.2. 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 Tablets 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.

4.2. 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.

5. TOXICOLOGY

No new data.

6. CLINICAL PHARMACOLOGY

To support the application, the applicant has submitted two single dose bioequivalence studies one fed and one fasted.

STUDY CPB 021-2006

A randomized, single dose, open-label, two-treatment, two-period, two-sequence, crossover bioequivalence study on Risperidone lmg tablets, (Wockhardt Limited, India) compared with Risperda1 1mg tablets, (Janssen - Cilag SPA, Latina, Italy) in 42+4 (standby) normal, adult, human subjects under fasting conditions.

Study design

A comparative, randomised, two-way, two-period, single dose crossover study of conventional design to assess the relative bioavailability of Wockhardt's and Janssen-Cilag's risperidone 1mg tablets. The study consisted of two treatment phases separated by a 20 day wash-out period. 42 +4 (standby) healthy male volunteers entered the study and were assigned to the treatment sequence according to the randomisation schedule, which was balanced for sequence and appears random.

Subjects received a single dose of 1mg orally of either the applicant's test product or the reference product Risperdal. Administration of the product was in accordance with the SPC.

Serum drug levels were followed for 96 hours following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max}. The washout period between phases was sufficiently long at 20 days.

Test and reference products

Test product (A):	Risperidone 1 mg tablets (Manufactured by Wockhardt Limited, India)
Reference product (B):	Risperdal® 1 mg tablets (Manufactured by Janssen – Cilag SpA, Latina, Italy)

Assessor's comment:
The comparator product is an EU product to which essential similarity is claimed and is therefore satisfactory in principle.

Population(s) studied

46 healthy fasted adult male volunteers were randomised and 37 completed the study.

Assessor's comment:
No concerns are raised regarding subject disposition.
All subjects that failed to complete the study and were excluded from the analyses did not receive study medication in period 2. Hence there is no potential for bias. The reasons for these dropouts are satisfactory. The other protocol violations detailed in the study report are not of concern and their data were used in the analyses, which is appropriate.

Results

Pharmacokinetic parameters for parent drug and the 9-OH active metabolite (log-transformed values; geometric mean)

Table No.10: Summarized statistical results of Risperidone based on ln-transformed data in 37 subjects (01 to 17, 19 to 27, 29, 30, 35, 38 & 40 to 46).

Parameter	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)
Geometric LSM*:			
A	9.62	55.75	57.18
B	9.30	54.69	56.63
Geometric LSM Ratio:			
A/B (%)	103.45 %	101.95 %	100.98 %
90% Confidence Interval:			
A Vs. B			
Lower Limit	95.70 %	94.86 %	94.03 %
Upper Limit	111.83 %	109.56 %	108.44 %
p-values (ANOVA):			
Sequence	0.9001	0.8337	0.8238
Subject (seq)	<0.0001	<0.0001	<0.0001
Period	0.9632	0.2197	0.2053
Formulation	0.4669	0.6541	0.8189
Intra-subject Variability:			
CV %	20.01 %	18.49 %	18.29 %
Power (%):	99.60 %	99.86 %	99.88 %

* Geometric LSM has been taken as the antilog (or exponential) of the least square mean (LSM) of the ln-transformed data.

Figure No. 4a: Linear Mean Plasma Concentration Time Curve for Risperidone under fasting conditions.

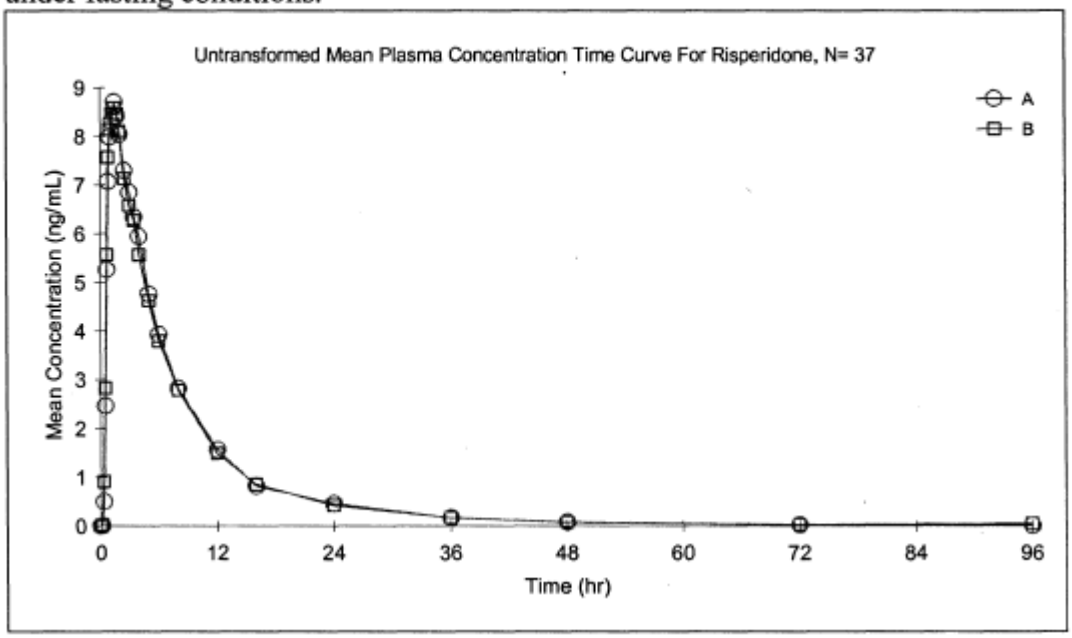
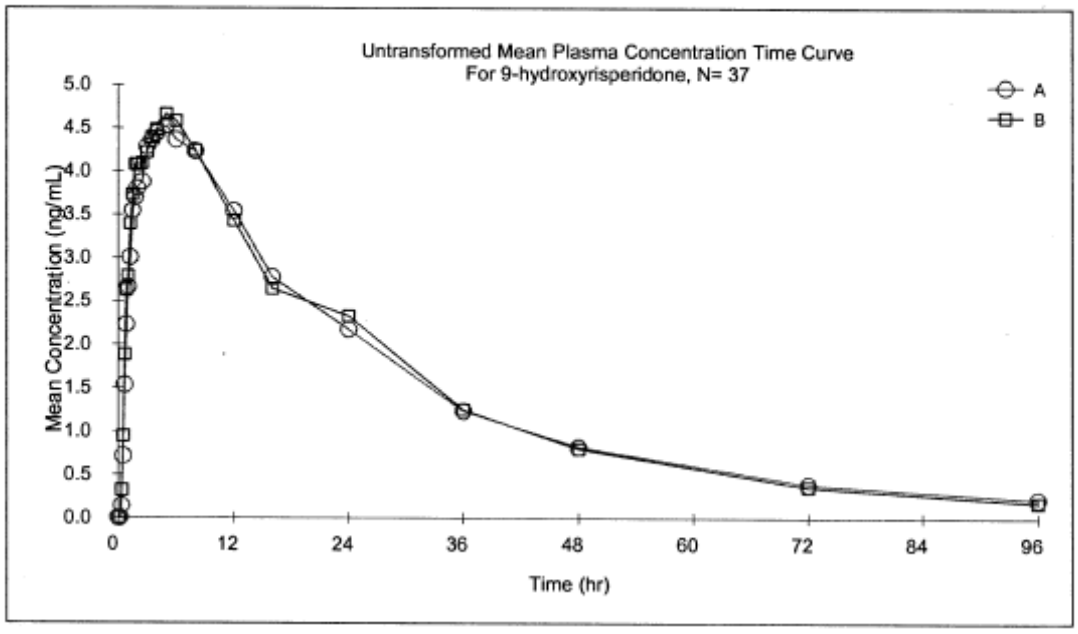


Figure No. 5a: Linear Mean Plasma Concentration Time Curve for 9-hydroxyrisperidone under fasting conditions.



Bioequivalence conclusion in the fasted state

Bioequivalence has been shown according to standard criteria.

CPB-021-2006: A randomized, single dose, open-label, two-treatment, two-period, two sequence, crossover bioequivalence study on Risperidone lmg tablets, (Wockhardt Limited, India) compared with Risperdal 1mg tablets, (Janssen - Cilag SPA, Latina, Italy) in 32 (28+4 standby) normal, adult, human subjects under fed conditions.

Risperidone Film Coated Tablets are Immediate Release products and in the EU there is no requirement for demonstration of bioequivalence in the fed state. Risperidone absorption is not affected by food. Nevertheless a study intended to demonstrate this has been submitted. It has been fully assessed as it is relevant data but full details will not be presented here as it is not pivotal to the application.

The design and conduct of the study were essentially the same as for the fasted study except that a standard high fat meal was taken prior to dosing. 32 subjects entered the study and 30 completed the 2 periods. Only 28 were included in the PK and statistical analyses because this was specified in the protocol (28+4 standby subjects). However subject nos. 10 & 24 were replaced with subject nos. 30 & 31, since the sequence was same as that of corresponding withdrawn subjects. The following is the relevant pre-specified rule from the trial protocol:

Samples from first 28 subjects (or all completed subjects when total less than 28) will be assayed. In the event of dropout or withdrawal from the first 28 subjects, samples from the next standby subject having the same sequence as that of dropout/withdrawal, will be analyzed. If necessary, an unequal number of subjects per sequence will be statistically analyzed.

The procedure followed, whilst not optimal (it would be preferable for the protocol to have specified that the analysis include all 30 subjects) is therefore according to protocol and acceptable.

Table No. 2 a: Summary of PK & Statistical Results calculated for Risperidone in 28 subjects (01 to 09, 11 to 23, 25 to 28, 30 & 31)

Parameter (units)	Geometric Least Squares Mean N = 28			90 % Confidence Interval	Intra-subject variability CV (%)	Power (%)
	Test (A)	Reference (B)	% Ratio (A/B)			
C_{max} (ng/mL)	9.02	8.16	110.48 %	100.21 % - 121.79 %	21.63 %	96.20 %
AUC_{0-t} (ng.hr/mL)	57.93	54.46	106.38 %	99.19 % - 114.09 %	15.44 %	99.89 %
$AUC_{0-\infty}$ (ng.hr/mL)	59.80	56.32	106.17 %	99.03 % - 113.83 %	15.37 %	99.89 %

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

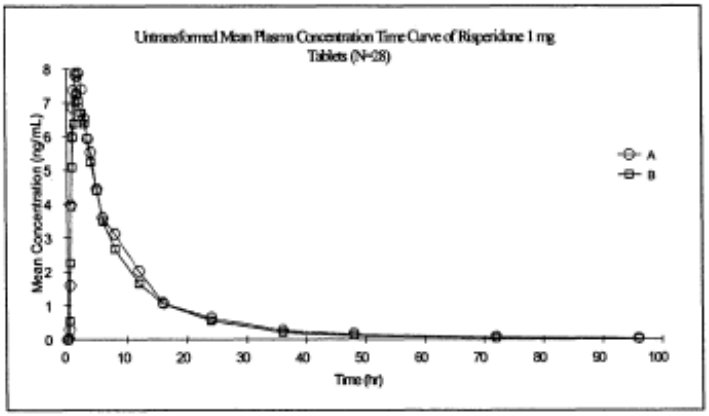


Figure No. 1b: Semi Log transformed Mean Plasma Concentration Time Curve for Risperidone

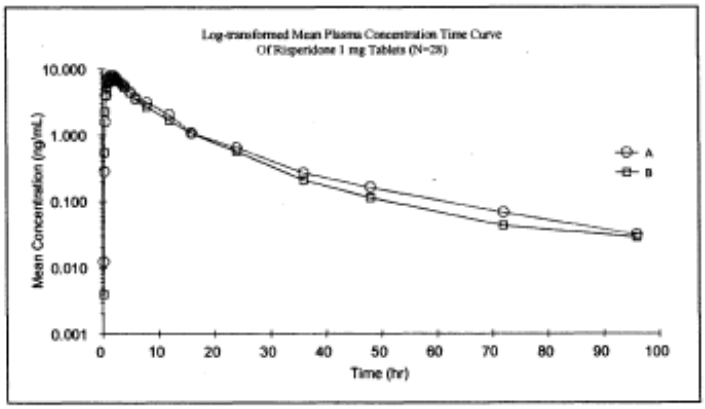


Table No. 2 b: Summary of PK Results calculated for 9-hydroxyrisperidone in 28 subjects (01 to 09, 11 to 23, 25 to 28, 30 & 31)

Parameter (units)	Geometric Mean	
	Test (A)	Reference (B)
C_{max} (ng/mL)	3.48	3.20
AUC_{0-t} (ng.hr/mL)	103.13	100.28
$AUC_{0-\infty}$ (ng.hr/mL)	111.03	108.12

Bioequivalence conclusion in the fed state
Bioequivalence has been shown according to standard criteria.

Pharmacokinetic conclusion

Based on the submitted bioequivalence study Risperidone Film Coated Tablets 1mg is considered bioequivalent with Risperdal®1mg Film Coated tablets (Janssen Cilag, IT) for the parent drug. The test/reference 90% confidence intervals provided for the 9-OH active metabolite in the fasted bioequivalence study are all well within 80-125% and confirm bioequivalence for the metabolite. The results of this study with the 1mg formulation can be extrapolated to other strengths 0.5mg/2mg/3mg/4mg/6mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

7. EFFICACY

No new data.

8. SAFETY

No new data.

9. EXPERT REPORTS

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

10. PATIENT INFORMATION LEAFLET (PIL)

This is satisfactory.

11. LABELLING

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

12. APPLICATION FORM (MAA)

The MAAs are medically satisfactory.

13. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPCs are essentially identical to the current approved SPCs for the reference products and are satisfactory.

14. DISCUSSION

The requested indications and other SPC details are consistent with current originator SPC. Bioequivalence to the reference product is established.

15. MEDICAL CONCLUSION

Marketing Authorisations may be granted for these preparations.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome