IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0688/006/001
Case No: 2012623

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Chanelle Medical

Loughrea, **Co. Galway**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Risperidone 0.25 mg Film-Coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **15/09/2006** until **14/09/2011**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 0.25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.25 mg of risperidone.
Also contains Lactose and Sunset Yellow (E110)

For a full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

0.25 mg: Light brown colour, round, scored film coated tablets.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Risperidone is suitable for the treatment of a great variety of patients with schizophrenia, including first episodes, acute exacerbation of schizophrenia, chronic schizophrenia and other psychotic situations in which positive symptoms are dominant (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness) and/or negative symptoms (such as blunted effect, social withdrawal, poverty of speech).
Risperidone relieves the affective symptoms (such as depression, feelings of guilt, anxiety) associated with schizophrenia.

Risperidone is also effective in the maintaining of clinical improvement during prolonged treatment in patients who show initial response to the treatment. Risperidone is suitable for the treatment of serious behavioural disturbance in patients with dementia whose symptoms, such as aggressiveness (physical and verbal violence), motor activity disturbance (agitation, wandering) or prominent psychotic symptoms and lead to suffering, incapacity, potential danger or self-harm of the patient.

Risperidone is also indicated as adjunctive therapy to mood stabilizers in the acute treatment of manic episodes associated with bipolar disorders. These episodes are characterised by symptoms such as elevated, expansive or irritable mood, excessively "high" or euphoric feelings, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility or poor judgement, including disruptive or aggressive behaviour.
Risperidone is indicated in the treatment of conduct and other disruptive behaiour disorders in children, adolesents and adults with impaired social, academic or occupational functioning, in whom challenging behaviours (e.g. aggression, impulsiveness, and self-injury) are prominent.

Risperidone is also suitable for the treatment of autism in children and adolescents.

4.2 Posology and method of administration

4.2a Schizophrenia

Acute and chronic treatment for schizophrenia
Adults and children over 15: Risperidone can be administered once or twice per day. To avoid risk of postural hypertension, the dosage should be titrated up gradually. Treatment is introduced at 2 mg per day. The dosage is increased to 4 mg on the second day. After this, the dosage can be maintained or further individualised as needed. The optimal dosage is normally 4-6 mg per day. For certain patients, a slower titration phase and a lower maintenance dose may be appropriate. Treatment of schizophreniform syndrome should continue for a maximum of 6 months.

Doses above 10mg/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 16mg /day have not been extensively evaluated for safety and therefore should not be used.

Elderly: A starting dose of 0.5mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily.
Patients should be monitored and treatment reviewed at regular intervals.
If the optimal dosage has been achieved, it may be preferable to change to one dose per day.

Children: Insufficient experience in treating children under 15 years of age.

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

4.2b Behavioural Disturbances in Patients with Dementia

A starting dose of 0.25 mg twice daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg twice daily, not more frequently than every other day, if needed. The optimum dose is 0.5 mg twice daily for most patients. Some patients, however, may benefit from doses up to 1 mg twice daily. Once patients have reached their target dose, a once daily dosing regimen can be considered. The patients condition should be reassessed regularly, and the confined use justified on an ongoing basis.

4.2c Bipolar Mania

A starting dosage of 2mg once daily is recommend. This can be individually adjusted by increments of up to 2mg/day not more frequently than every other day. Most patients will benefit from doses between 2 and 6 mg/day.

Treatment with Risperidone should be reviewed regularly and discontinued if no benefit is seen or intolerance occurs.

Because patients with bipolar disorder have a low threshold for tardive dyskenesia, the need for continued treatment with Risperidone should be reassessed regularly.

4.2d Conduct and other disruptive behaviour disorders

Patients weighing more than 50 kg
A starting dose of 0.5mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5mg once daily not more frequently than every other day, if needed.
The optimum dose is 1mg once daily for most patients. Some patients, however, may benefit from 0.25mg once daily while others may require 2 mg once daily.

Patients weighing less than 50 kg
A starting dose of 0.25mg once daily is recommended, which can be individually adjusted by increments of 0.25mg once daily not more frequently than every other day, if needed.

The optimum dose is 0.5mg once daily for most patients, although some patients may benefit from 0.25mg once daily while others may require 2 mg once daily.

As with all symptomatic treatments, the continued use of Riperidone must be evaluated and justified on an on-going basis.

4.2e Autism (children aged 5 or over and adolescents)
The dosage of Risperidone should be individualised according to the needs and response of the patient.

Dosing should be initiated at 0.25 mg per day for patients <20 kg and 0.5 mg per day for patients ≥20 kg. On Day 4, the dose may be increased by 0.25 mg for patients <20 kg and 0.5 mg for patients ≥20 kg. This dose should be maintained and response should be assessed at approximately Day 14. Only in patients not achieving sufficient clinical response should additional dose increases be considered. Dose increases may proceed at 2-week intervals in increments of 0.25 mg for patients <20 kg or 0.5 mg for patients ≥20 kg.

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

Doses of Risperidone in Pediatric Patients With Autistic Disorder
(by total mg/day)

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

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

For prescribers preferring to dose on a mg/kg/day basis the following guidance is provided.
Doses of Risperidone in Pediatric Patients With Autistic Disorder
(by mg/kg/day)

Weight Categories	Days 1-3	Days 4 – 14+	Increments if Dose Increases are Needed	Dose Range
All	0.01mg/kg/day	0.02mg/kg/day	+0.25 mg + 0.01mg/kg/day at ≥2 week intervals	0.02mg/kg/day – 0.06mg/kg/day

Risperidone can be administered once daily or twice daily.
Patients experiencing somnolence may benefit from a switch in dosing from once daily to either once daily at bedtime or twice daily.
Once sufficient clinical response has been achieved and maintained, consideration may be given to gradually lowering the dose to achieve the optimal balance of efficacy and safety. There is insufficient evidence from controlled trials to indicate how long the patient with Autistic Disorder should be treated with Risperidone.

Method of administration
Oral use.

Switching from other Antipsychotics
For change in therapy: In the case of a change from another antipsychotics to Risperidone, a slow de-escalation of the former treatment should be carried out in order to reduce the risk of withdrawal effects from the former treatment.

When changing from depot antipsychotics, the Risperidone treatment is introduced at the time of the next planned injection. The need for continued treatment with anticholinergics should be reassessed regularly.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial titration period of the dose to be administered.
Risperidone should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolaemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see dosage and administration). A dose reduction should be considered if hypotension occurs.

Hyperglycemia and deterioration of existing diabetes have been reported in very rare cases during treatment with risperidone. Adequate follow up is recommended for diabetes patients and patients at risk of developing diabetes (see also section 4.8 Side Effects).

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face.
It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia.

Risperidone should therefore have a reduced risk of inducing tardive dyskinesia as compared to classical neuroleptics. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

As with other neuroleptics, rare cases of Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated Creatine Phosphokinase (CPK) levels have been reported. In such an event, all antipsychotic drugs, including Risperidone, should be discontinued.

Physicians should assess the risks versus the benefits when prescribing Risperidone, to patients with Lewy body dementia or Parkinson's disease since they may be at increased risk of neuroleptic malignant syndrome or a worsening of Parkinson-like symptoms.

For posology recommendations in elderly patients, patients with renal and liver disease and patients with dementia, please see recommended doses and dosage schedule.

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, some of which were fatal and transient ischaemic attacks) in patients treated with risperidone, compared with placebo. Cerebrovascular adverse events (CVAEs) occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo.

Prior to treatment, physicians should carefully consider 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 Cerebrovascular accidents/transient ischaemic attacks (CVA/TIA), or vascular co-morbidities such as hypertension and cardiovascular disease.

These patients should be closely monitored during treatment and patients/caregivers advised to immediately report signs and symptoms of potential CVAEs, such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. Patients presenting with such symptoms should be promptly evaluated and treatment discontinued, if appropriate.

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 to refrain from excessive eating in view of the possibility of weight gain.

Patients with rare hereditary problems of galactose intorlerance, 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.

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

Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of risperidone. A similar effect may 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 increased 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 inhibitors, galantamine and donepezil, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active 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.

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

The combined use of psychostimulants (e.g. methylphenidate) with Risperidone in children and adolescents did not alter the pharmacokinetics and efficacy of Risperidone. The incidence of somnolence was reduced when psychostimulants were used concomitantly.

4.6 Pregnancy and lactation

The safety of Risperidone for use during human pregnancy has not been established. Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and central nervous system-mediated effects were observed. No teratogenic effect of risperidone was noted in any study. 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 this excretion also occurs 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. In children and adolescents, mild and transient sedation has been reported more frequently than in adults.
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 adverse events, including cerebrovascular accidents (some of which were fatal), and transient ischaemic attacks, have been reported during treatment with Risperidone. (See also Section 4.4, Special warnings and special precautions for Use.)

Risperidone has a lower propensity to induce extrapyramidal symptoms than classical neuroleptics. However, in some cases the following extrapyramidal symptoms may occur: tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia. If acute in nature, these symptoms are usually mild and are reversible upon dose reduction and/or administration of antiparkinson medication, if necessary.

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, the following have occasionally been reported in psychotic patients: water intoxication due to either polydipsia or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH); tardive dyskinesia, Neuroleptic Malignant Syndrome, body temperature dysregulation and seizures.

The following adverse events have been reported as very common in children and adolescents with conduct disorders: somnolence, headache, hyperprolactinaemia, weight increase**.**

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

4.9 Overdose

Overdosages of up to 360 mg have been reported. 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

Pharmacotherapeutic group: Antipsychotics
ATC code: N05AX08

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, an activity which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce 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. The absorption is not affected by food and thus Risperidone can be given with or without meals.

Risperidone is partly metabolised by cytochrome P-450 IID6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. Another metabolic pathway of risperidone is N-dealkylation.

The metabolism of risperidone is dependent upon the metabolism of the individual, which entails that slow or fast metabolisers demonstrate different quotas of risperidone/9-hyrdoxy risperidone. However, because precursor and metabolite have equivalent effects, the degree of metabolism lacks therapeutic significance.

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

Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4-5 days of dosing. Risperidone plasma concentrations are dose-proportional within the therapeutic dose range. Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and $alpha_1$-acid glycoprotein. The plasma protein binding of risperidone is 88%, that of 9-hydroxy-risperidone approximately 77%. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the dose. The remainder are inactive metabolites.

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.

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

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 Starch Glycollate,
Lactose monohydrate,
Microcrystalline cellulose,
Colloidal Silica anhydrous,
Magnesium stearate,
Sodium lauryl sulphate,
Pregelatinised maize starch.
Hypromellose
Titanium dioxide (E171)
Macrogol
Iron Oxide Yellow (E172)
Sunset Yellow (E110)
Brilliant Blue (E133)

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

2 Years

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions.

6.5 Nature and contents of container

Blister composed of clear colourless PVC/PDVC and plain aluminium foil. The strips are packed in cardboard cartons containing 6, 20, 28, 30, 50, 56, 60 and 500 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Chanelle Medical
Loughrea
Co. Galway
Ireland

8 MARKETING AUTHORISATION NUMBER

PA/688/6/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 15th September 2006

10 DATE OF REVISION OF THE TEXT