IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0915/014/002
Case No: 2035485

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

Helsinn Birex Therapeutics Ltd

Damastown, **Mulhuddart**, **Dublin 15**, **Ireland**

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

Radlinn 1mg 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 **02/05/2008** until **01/05/2013**.

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

Radlinn 1mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1mg of risperidone and 57.65mg of lactose monohydrate

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

White, capsule shaped, biconvex film-coated tablet with “1” on one side and “RSP” on the other side with a score line separating the “R” from the “SP”.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Risperidone is intended for the treatment of schizophrenia.

- Risperidone is also effective as maintenance treatment of schizophrenia in patients who responded to initial treatment with risperidone.

- Risperidone is indicated for the treatment of moderate to severe manic episodes.

4.2 Posology and method of administration

Method of administration
Oral. The tablets should be taken with an adequate quantity of liquid (e.g. a glass of water) with or without food.

Children and young people up to the age of 15 years
Radlinn Film-Coated Tablets are not recommended for use in children and young people below age 15 due to a lack of data on safety and efficacy.

4.2.a Schizophrenia

Changing over from treatment with other antipsychotic drugs to risperidone
In this case it is recommended to gradually reduce the previous medication and at the same time introduce treatment with risperidone. When changing over from depot antipsychotic drugs in justified cases changing over to risperidone can take place at the time of the next planned injection.

The need to continue initiated treatment of extrapyramidal symptoms (anti-Parkinson medication) has to be assessed continuously.

Adults and young people over the age of 15 years
Risperidone can be taken once or twice daily.

The treatment starts with a dose of 2 mg daily. On the second day the dose can be increased to 4 mg. This dose can be adjusted in accordance with individual requirements. The optimum daily dose is usually 4-6 mg daily. In some patients a slower titration phase, a lower starting dose and maintenance dose commensurate therewith may be necessary.

In clinical studies it has not been shown that doses over 10 mg have a greater antipsychotic effect, but may however increase the risk of extrapyramidal symptoms. The safety of doses above 16 mg daily has not been verified, and the dosages should not therefore exceed this level.

To achieve an additive sedative effect is it recommended to supplement the treatment with other preparations (e.g. benzodiazepines) rather than increasing the dose of risperidone.

Elderly
A starting dose of 0.5 mg twice daily is recommended. Depending on the individual response each dose can be increased by 0.5 mg to achieve a dose of 1-2 mg twice daily. Clinical experience in older patients is limited and therefore particular care is required when administering risperidone.

Renal and hepatic impairment
In patients with renal or hepatic impairment, risperidone must be used with care as there is only limited experience of the treatment of this group of patients.

The recommended starting dose is 0.5 mg twice daily. Depending on the individual response the dose can be increased to 1 – 2 mg twice daily (with increments from 0.5 mg twice a day).

4.2.b Manic episodes

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.

Children and adolescents under the age of 18
There is no experience available of the treatment of manic episodes in children and adolescents under the age of 18 years.

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 hepatic impairment
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.

4.3 Contraindications

Risperidone is contraindicated in patients with a known hypersensitivity to risperidone or to any of the excipients.

4.4 Special warnings and precautions for use

Older patients with dementia
There is an increased risk of cerebrovascular side effects, including CVAs and TIAs in patients with dementia. In clinical studies a threefold increase in cerebrovascular side effects was seen in patients treated with risperidone compared with patients treated with placebo (3.4% versus 1.1% respectively). It is therefore recommended not to prescribe Risperidone to dementia patients with a history of CVA/TIA, hypertension or diabetes.

Overall Mortality
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 Risperdal. In placebo-controlled trials with Risperdal in this population, the incidence of mortality was 4.0% for Risperdal treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100).

Concomitant use with Furosemide
In the Risperdal placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90. Odds ratio [95% confidence interval] was 1.82 [0.65, 5.14]). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.
No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAE)
In placebo-controlled trials in elderly patients with dementia was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischaemic attacks), including fatalities in patients (mean age 85 years, range 73-97) treated with Risperdal, compared to patients receiving 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 Risperdal (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of 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.

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)
Treatment with drugs with an antagonistic effect on dopamine receptors can cause retarded dyskinesia characterised by involuntary movements, in particular of the muscles of the tongue, mouth or face.

There have been reports of the occurrence of extrapyramidal symptoms as risk factors for the development of retarded dyskinesia. If symptoms of retarded dyskinesia occur in patients, the discontinuation of any antipsychotic treatment should be responsibly considered.

Neuroleptic Malignant Syndrome (NMS)
In the case of treatment with classic neuroleptics, a malignant neurotic syndrome may occur manifesting itself as hyperthermia, tachypnoea, perspiration, muscle stiffness, autonomous instability, consciousness disorders, leukocytosis and increased plasma levels of creatine phosphokinase. The occurrence of rhabdomyolysis with associated renal insufficiency is usually life-threatening.

In the event of the occurrence of a malignant neurotic syndrome antipsychotic treatment should be suspended. In addition to the usual supportive measures (external cooling and rehydration) anticholinergic drugs and benzodiazepines are usually given. In severe cases these agents may not be sufficiently effective and dantrol and/or dopamine agonists must be administered. If this treatment is not effective either, or in the event of a threat to life electroconvulsive treatment must be given.

Hyperglycaemia
Hyperglycaemia or aggravation of pre-existing diabetes have been reported in very rare cases during treatment with risperidone. It is advised to clinically monitor patients with diabetes and patients at increased risk of developing diabetes mellitus (see also section 4.8 Undesirable effects).

Epilepsy
Like other antipsychotics, risperidone can lower the stimulus threshold. In epilepsy patients risperidone must therefore be administered with the necessary caution.

Weight gain
In view of the possibility of weight gain the patients should be advised about their eating patterns.

Lewy body dementia and Parkinson´s disease
In the event or risperidone being prescribed to patients suffering from Lewy body dementia or Parkinson´s disease the disease symptoms may worsen. The risk of malignant neuroleptic syndrome may also increase.

It is known that classic neuroleptics lower the paroxysmal threshold. Care must be taken when treating epileptic patients.

Withdrawal symptoms
In rare cases, after suddenly stopping treatment with high doses of antipsychotic preparations, acute withdrawal syndromes have been described, including nausea, vomiting, perspiration and insomnia. The return of psychotic symptoms and the development of disorders with involuntary movements (such as akathesia, dystonia and dyskinesia) can occur. Treatment must be discontinued gradually.

Use in children and adolescents under 15
There is no clinical experience of the treatment of children under the age of 15 years with risperidone and therefore its use is not recommended for this group of patients.

Renal and hepatic impairment
Administration to older patients and patients with liver and kidney disease is described in section 4.2 Posology and method of administration.

Aggravation of symptoms
Paradoxically enough, antipsychotic drugs can aggravate symptoms such as excitation, agitation and aggressiveness. In the case of these symptoms, with risperidone, as with other antipsychotic drugs, a reduction in the dose or discontinuation of the treatment may be necessary.

Hyperprolactinaemia
Risperidone may only be used with care in patients with hyperprolactinaemia which is not drug-related. Particular care is necessary in the case of patients with possible prolactin-dependent tumours (e.g. breast cancer).

Lactose content of tablets
As the coated tablets contain lactose they should not be taken by patients with rare hereditary intolerance to galactose, Lapp lactase deficiency or glucoso-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

The risks of using risperidone in combination with other medicinal products have not been systematically studied. Care must be taken when combining risperidone with other agents that act on the central nervous system. Antipsychotics intensify the action of, among other things, alcohol, opioids, antihistamines and benzodiazepines. Alcohol consumption must therefore be advised against.

Risperidone can antagonise the effect of levodopa and other dopaminergic agonists.

Carbamazepine reduces the plasma levels of risperidone and its active metabolite. Similar effects can also be observed in other preparations that metabolise enzymes in the liver. At the end of treatment with carbamazepine or other preparations that induce liver enzymes the level of the risperidone dose must be reappraised and whether it is necessary to reduce the dose.

Phenothiazines, tricyclic antidepressants and some beta-blockers can increase the plasma concentration of risperidone but have no effect on the antipsychotically active fraction (see section 5.2 Pharmacokinetic properties). Amitriptyline has no influence on the pharmacokinetics of risperidone or the antipsychotically active fraction. Cimetidine and ranitidine increase the bioavailability of risperidone but only have a marginal effect on the antipsychotically active fraction.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone by inhibiting cytochrome P-450 1106. However, through this inhibition less of the active metabolite is produced as a result of which the antipsychotically active fraction (unmodified risperidone and active metabolite) increases less. When fluoxetine or paroxetine are started or stopped the dose of risperidone must be reappraised.

Erythromycin, a CYP 3A4 inhibitor has no effect on the pharmacokinetics of risperidone and the antipsychotically active fraction. The cholinesterase inhibitors galantamine and donezepil show no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotically active fraction.

Risperidone has no clinically relevant effect on the pharmacokinetics of lithium, valproinic acid or digoxin.

The anti-α1 -adrenergic action (particularly of phenothiazines) can produce an intensification of the blood pressure-lowering effect of phenoxybenzamine, labetaiol and other α-blocking sympathicolytic drugs, as well as of methyldopa, reserpine and other centrally acting antihypertensives.

In contrast, the blood pressure lowering effect of guanethidine is blocked.

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

Interactions relating to furosemide in older patients with dementia are described in section 4.4.

Combining certain antipsychotic drugs with diuretics such as furosemide and chlorothiazide can sharply increase the elimination water, sodium and sometimes also chloride. Antacids reduce the oral uptake of antipsychotic drugs. Drugs that induce liver enzyme activity (barbiturates, phenytoin and carbamazepine) accelerate the breakdown of antipsychotic drugs

The simultaneous use of other antipsychotics, lithium, antidepressants, anti-Parkinson´s drugs and drugs with a central anticholinergic action increases the risk of the development of retarded dyskinesia. Risperidone has no clinically significant effect on the pharmacokinetics of lithium and valproate.

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

4.6 Pregnancy and lactation

Pregnancy
Risperidone has harmful pharmacological effects on the new born child. Reversible extrapyramidal symptoms in the neonate were observed following post-marketing use of risperidone during the last trimester of pregnancy.

In studies with laboratory animals risperidone was not teratogenic, but certain types of reproduction toxicity were found (see section 5.3).

Risperidone should not be used during pregnancy unless clearly necessary, ie if the treatment benefit to the mother outweighs the possible risk to the foetus or newborn child.

Breastfeeding
Risperidone and its active metabolite 9-hydroxy-risperidon pass into the mother´s milk in such quantities that an effect on the infant is likely during the administration of therapeutic doses to the mother. Risperidone must not be taken during breastfeeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Antipsychotic agents such as risperidone can influence the ability to react. Patients must therefore be advised not to drive motor vehicles or use machines until the individual reaction to risperidone has been ascertained.

4.8 Undesirable effects

In many cases it is difficult to distinguish undesirable effects from the signs of the underlying illness. In connection with risperidone the following undesirable effects have been reported.

Undesirable effects have been listed by system organ classes and frequency.

Frequency has been ranked as follows:

- very common >1/10,
- common >1/100, <1/10,
- uncommon >1/1000, <1/100,
- rare >1/10,000, <1/1000,
- very rare >1/10,000, including isolated reports

Infections and infestations
Uncommon: rhinitis

Blood and the lymphatic system disorders
Very rare: neutropenia and thrombocytopenia

Endocrine disorders
Uncommon: dose dependent increase in prolactine levels

Metabolism and nutrition disorders
Very rare: hyperglycaemia, aggravation of existing diabetes (see section 4.4)

Psychiatric disorders
Common: insomnia, agitation, fear.
Uncommon: decreased concentration

Nervous system disorders
Common: headache, sedation
Uncommon: tremor, bradykinesia, acathisia, dizziness

Eye disorders
Uncommon: blurred vision

Cardiac disorders
Uncommon: reflex tachycardia. This undesirable effect has been reported with higher initial doses.
Rare: QT prolongation, ventricular arrhythmias (VT, VF), cardiac arrest, Torsdaes de pointes
Very rare: Hypertension

Vascular disorders
Uncommon: orthostatic hypotension
Rare: cerebrovascular undesirable effects including CVA's and TIA's (see section 4.4).

Respiratory, thoracic and mediastinal disorders
Uncommon: hypersalivation

Gastrointestinal disorders
Uncommon: constipation, dyspepsia, nausea, abdominal pain
Very rare: vomiting

Skin and subcutaneous tissue disorders
Uncommon: rash and other hypersensitivity reactions
Very rare: angio-oedema

Muscoloskeleta and connective tissue disorders
Uncommon: rigidity, acute dystonia

Renal and urinary disorders
Very rare: enuresis

Reproductive system and breast disorders
Uncommon: erectile disturbances, ejaculatory disturbances, impotence men who previously did not have any sexual disturbances, orgasmic dysfunction.

Rare: galactorroe, gynaecomastia, cyclus disturbances in women and amenorrhea.
Very rare: priapism

General disorders and administration site conditions
Uncommon: somnolence, fatigue
Rare: Weight gain (see section 4.4)
Very rare: oedema

Investigations
Very rare: increased hepatic enzyme levels.

After long term use of antipsychotic medicinal products (months to years) dyskinesia may occur (especially tardive dyskinesia), during, as well as after treatment (see sections 4.4 and 4.5).
Like for traditional antipsychotic medicinal products some cases of water intoxication are observed. These were due to polydipsia or to the syndrome caused by inadequate secretion of antidiuretic hormone (SIADH). Furthermore rarely have been observed: convulsions, worsening of depression and dysphoria, disturbance of body temperature and malign neuroleptic syndrome (see section 4.4).

Cerebrovascular events
During treatment with risperidone cerebrovascular undesirable effects have been reported, including cerebrovascular events (CMP) and transitory ischaemic attacks (TIA). In placebo-controlled studies in older patients with dementia using risperidone (daily dose 0.5 - 2 mg) a threefold increase in the incidence of cerebrovascular undesirable effects, including CMP (some cases were fatal) and episodes of TIA were observed compared with placebo. The relative risk was 2.96 (95% reliability interval: 1.33-7.45). The average age of this population was 85 years, in a range from 73 to 97 years. The risk was not associated with the dose or length of treatment.

Summarising data from six placebo-controlled studies in older patients with dementia (> 65 years) demonstrated the rate of cerebrovascular undesirable effects (serious and non-serious) as 3.3% (33/989) in patients treated with risperidone and 1.2% (8/693) in patients receiving placebo.

Treatment with risperidone may cause a prolonged QT-interval. Cases of sudden death which may be cardiac in origin have been reported during risperidone treatment (see section 4.4).

4.9 Overdose

Symptoms
The symptoms of overdose correspond to the known desirable and undesirable pharmacological effects. The most common include tiredness, tachycardia, hypotension and extrapyramidal symptoms. The highest known overdose of risperidone was a dose of 360 mg. On the basis of current knowledge it is assumed that risperidone has a wide safety spectrum. In connection with overdose isolated cases of prolongation of the QT interval have occurred. In the event of acute overdose it must be ascertained whether simultaneous overdose with further preparations is involved.

Treatment
The airways must be kept open and adequate oxygen supply ensured. Gastric irrigation may be considered (after intubation if the patient is unconscious) as well as the administration of activated charcoal together with laxatives. Monitoring of cardiovascular function must be commenced immediately which must include continual ECG monitoring to diagnose possible arrhythmias.

There is no specific antidote to risperidone. Therefore primary supportive measures must be taken. Hypotension and possible circulatory collapse must be suitable treated with intravenous fluids and/or sympatomimetic drugs. In the event of severe extrapyramidal symptoms anticholinergic preparations must be given. The patient should be under close medical supervision until his/her condition has stabilised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics *ATC code:* N05A X08

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 alpha2-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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety and pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. No toxicity is observed other than those caused by the pharmacological action of the drug.

In vivo and *in vitro* animal models have shown that risperidone can increase QTc-intervals which can be associated with cardiovascular events.

Animal reproduction studies at pharmacologically active doses showed some toxicity in the mother with an increase in labour period and increase in post-natal deaths. These effects were related to the pharmacodynamic effects of risperidone. The impact on the postnatal development appeared to rely mainly on the pharmacodynamic impact on the mothers (for example sedation and reduced care for their young). This impact is not relevant for the assessment of potential risk in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Pregelatinised starch
Microcrystalline cellulose (E460)
Sodium lauryl sulphate

Colloidal anhydrous silica
Talc (E553b)
Magnesium stearate (E470b)
Hypromellose (E464)
Polyethylene glycol
Titanium dioxide (E171)

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium foil/PVC/PVdC blisters in cartons of 20, 28, 50, 56 or 60 tablets

Note: Not all packs might 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 requirements

7 MARKETING AUTHORISATION HOLDER

Helsinn Birex Therapeutics Ltd
Damastown
Mulhuddart
Dublin 15
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8 MARKETING AUTHORISATION NUMBER

PA 915/14/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd May 2008

10 DATE OF REVISION OF THE TEXT