IPAR

Irish Medicines Board

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Risperidone 1mg/ml Oral Solution
Risperidone

This module reflects the scientific discussion for the approval of Risperidone 1mg/ml Oral Solution. The procedure was finalised at Day 90 on 11th February 2009. For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

This mutual recognition application concerns a generic version of risperidone and is submitted under the provisions for abridged applications under Art.10.1 (a) (iii) of Directive 2001/83/EC as amended, and is hence a "generic" application.

With Ireland as the Reference Member State, Chanelle Limited, Ireland is applying for the Marketing Authorisation for Risperidone solution 1 mg/ml in Germany and Poland.

Risperidone solution 1 mg/ml is an oral solution that was developed to have pharmaceutical qualities as close as possible to the innovator product Risperdal® solution 1 mg/ml (Janssen-Cilag). Essential similarity is being claimed because the two products have the same qualitative and quantitative composition in terms of the active principle and the same pharmaceutical form. A bioequivalence study is not required in line with section 5.1.2 of Note for Guidance on the Investigation of Bioavailability and Bioequivalence – CPMP/EWP/QWP/1401/98.

II QUALITY ASPECTS

II.1 Introduction

The product is an oral solution of risperidone containing 1mg/ml of risperidone presented in a multi-dose presentation. The innovator product of this generic is well-established in the European market.

The active substance, tartaric acid, benzoic acid and purified water form a clear and colourless solution. Tartaric acid is used as an acidifying agent. Benzoic acid is used as a preservative. Concentrated Hydrochloric Acid is used to adjust the solution to an optimum pH. The product is presented in an amber glass bottle. An appropriate plastic dosing pipette is supplied as part of the product.

II.2 2.2 Drug Substance

The drug substance, risperidone, is an established drug substance described in the European Pharmacopoeia (Ph. Eur.). It is manufactured in accordance with Good Manufacturing Practice. The drug substance manufacturer has demonstrated its acceptability by successfully using the Ph. Eur. CEP procedure.
The drug substance specification is considered adequate to control the quality and meets the current pharmacopoeial requirements. Batch analytical data for three batches are provided.
EDQM have approved a re-test date of three years.

II.3 Medicinal Product

II.3.1 Composition

The product is a clear, colourless oral solution in Purified Water with pH adjusters and a preservative. Each ml contains 1mg risperidone and the excipients tartaric acid, benzoic acid and hydrochloric acid for pH adjustment.
Container / Closure System
The solution may be presented in amber bottles of 30ml, 60ml, 100ml or 120ml, each bottle is supplied with an approved dosing pipette.

II.3.2. Pharmaceutical Development

The product is an established pharmaceutical form and is adequately described in accordance with the relevant European guidelines.
The aim of the development was to produce a stable product essentially similar to the innovator product, Risperdal 1mg/ml Oral Solution, marketed by Janssen. The product development is well described in line with the relevant European Guidelines.
In accordance with section 5.12 of note for guidance on bioavailability & bioequivalence CPMP/EWP/QWP/1401/98 a bioequivalence study is not required for this dosage form.

II.3.3 Method of Preparation of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) using conventional manufacturing techniques. The manufacturing process is considered adequately validated.

II.3.4. Control of Excipients

All excipients comply with their respective European Pharmacopoeia monographs. There are no excipients of human or animal origin used in the manufacture of this product. There are no novel excipients used in the manufacture of this product.

II.3.5. Control of Finished Product

The finished product specification is adequate to control the relevant parameters of this product.

The specifications are in line with those required for similar product types as per *Q6 CPMP/ICH/376/96 note for guidance on specifications.* Release specifications for the drug substance are based on the substance's Ph. Eur. Monograph. The analytical methods are described in sufficient detail and are supported by validation data.
Batch analytical data have been provided demonstrating compliance with the specification and thus demonstrates the ability to manufacture finished product consistent quality.

II.3.6 Packaging Materials

A type III amber glass bottle with a child-resistant and tamper-evident polypropylene/low density polyethylene cap is used. A plastic dosing pipette with a polystyrene plunger and Low density polyethylene barrel and piston is supplied as part of the product. The dosing pipette has a CE mark and is calibrated appropriately to allow accurate dose dispensing.

Certification has been presented that packaging materials complies with suitable Ph. Eur. glass & plastic requirements and that the caps comply with the requirements of 2002/72/EC relating to plastic materials intended to come in contact with food.

II.3.7.Stability Tests on Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product over 3 years. The product as packaged for sale should not be frozen but other than this does not require any special storage precautions prior to use.

An in-use stability study justifies a shelf-life of 4 months once opened.

The product has been shown to be incompatible with some beverages.
A study has identified three beverages; mineral water, orange juice or black coffee which are compatible and should be used if dilution is necessary. These are highlighted n the SPC.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The critical quality parameters of the product have been satisfactorily identified and controlled. Satisfactory chemical and pharmaceutical documentation has been provided allowing an assurance of consistent quality for Risperidone 1mg/ml oral solution.

III NON-CLINICAL ASPECTS

III.1 Introduction

Risperidone is widely available throughout Europe and the US. It is described in many standard formularies, including the British National Formulary, Martindale, Dollery, Goodman and Gilman and the Physician's Desk Reference. The safety of risperidone in man has been reviewed. The most frequent side effects are insomnia, anxiety, agitation, headache and anticholinergic side effects such as dry mouth and blurred vision. The proposed contraindications, precautions and warnings applied to this formulation of risperidone are the same as those applied to the reference product Risperdal (Janssen-Cilag) and are supported by the findings in the published literature.

III.2 Pharmacology

The pharmacology risperidone has been well established and is extensively reviewed in the literature.

III.3 Pharmacokinetics

No new pharmacokinetic studies were presented in support of this application. The pharmacokinetics of risperidone have been successfully established and documented within the literature and an appropriate and sufficient summary of these findings were presented. A summary of the clinical pharmacokinetics are presented in the clinical section.

III.4 Toxicology

No new toxicological studies were submitted in support of this application. The toxicology of risperidone is considered to have been well established with respect to acute and chronic toxicity by the extensive duration of clinical use.
Acute oral toxicity studies indicate LD_{50} values of 18.3 mg/kg in dogs and 113 mg/kg in rats. In the subchronic toxicity studies in rats and dogs, the major effects were mammary gland hypertrophy and changes in the male and female genital tracts attributable to hyperprolactinaemia. Risperidone is neither embryotoxic nor teratogenic in rats or rabbits. The central nervous system actions of risperidone resulted in a decreased nursing behaviour of the rat dams and a lower survival rate in their pups. There was no evidence of genotoxic potential in short term studies as demonstrated by the Ames reverse mutation test, mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila* or the chromosome aberration test in human lymphocytes or Chinese hamster cells. As expected for a potent D_2 antagonist, long-term carcinogenicity studies revealed prolactin-mediated endocrine disturbances with increased incidences of mammary gland, endocrine pancreas and pituitary gland neoplasia. No effect on the incidence of prolactin-independent neoplasia was observed. These studies were performed in Swiss albino mice (18 months duration) and Wistar rats (24 months duration) given up to 37.5 times the maximum recommended human dose on a mg/kg basis. The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unknown.

A review of risperidone exposure during pregnancy in humans showed no increased risk of spontaneous abortions, structural malformations or foetal teratogenicity with treatment. However, risperidone should be only used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

III.5 Ecotoxicity/environmental risk assessment

Risperidone Solution is an application according to Article 10(10 2001/83/EC (as amended)- generic application.

Risperidone is not a new drug substance and the brand leader Risperdal ® has been authorised in the EU for more than 10 years.
The marketing authorisation application is for a drug product which will not be administered at a higher dose level, or for a longer duration or for different indications than were previously in effect. There is no increased environmental risk associated with the introduction of this generic. Therefore no risk assessment has been performed

III.6 Discussion on the non-clinical aspects

Risperidone has been used in the clinical setting for an extensive period of time. The pharmacology, pharmacokinetics and toxicology (acute, chronic, reproductive etc.) have been well established. The lack of new studies presented in support of this application is considered justified and the company provided an extensive review of the literature and an appropriate assessment in support of this application. The safety and toxicological profile of the drug is considered established and no new studies were considered to be warranted.

IV CLINICAL ASPECTS

IV.1 Introduction

This mutual recognition application concerns a generic version of risperidone and is submitted under the provisions for abridged applications under Art.10.1 (a) (iii) of Directive 2001/83/EC as amended, and is hence a “generic” application.

With Ireland as the Reference Member State, Chanelle Limited, Ireland is applying for the Marketing Authorisation for Risperidone solution 1 mg/ml in Germany and Poland.

Risperidone solution 1 mg/ml is an oral solution that was developed to have pharmaceutical qualities as close as

possible to the innovator product Risperdal® solution 1 mg/ml (Janssen-Cilag). Essential similarity is being claimed because the two products have the same qualitative and quantitative composition in terms of the active principle and the same pharmaceutical form. A bioequivalence study is not required in line with section 5.1.2 of Note for Guidance on the Investigation of Bioavailability and Bioequivalence – CPMP/EWP/QWP/1401/98.

The indications for Risperidone are:

- Risperidone is indicated for the treatment of schizophrenia.
- Risperidone is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.
- Risperidone is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.
- Risperidone is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

The submitted documentation in relation to the proposed product is of sufficient high quality in view of the present European regulatory requirements. A clinical overview, which represents an adequate summary of the dossier, has been submitted.

IV.1.1 GCP aspects

The legal basis for this application for Marketing Authorisation for Risperidone Solution 1 mg/ml is according to Article 10(1) of Directive 2001/83/EC as amended – so called "generic application". A bioequivalence study is not required in line with section 5.1.2 of Note for Guidance on the Investigation of Bioavailability and Bioequivalence – CPMP/EWP/QWP/1401/98.

IV.2 Pharmacokinetics

Absorption

Risperidone is rapidly and completely (>97%) absorbed following oral administration and reaches peak plasma levels within 2 hours. Oral absorption is affected very little by food, Tmax being slightly later and bioavailability increasing by 11%. Cmax following an oral dose of 1 mg is 6-16 mg/L. There is some (20-35%) pre-systemic metabolism. Following intramuscular injection risperidone is rapidly and completely absorbed and reaches peak plasma concentration after 8-30 minutes.

The pharmacokinetics of risperidone are linear over the therapeutic dose range (1-16 mg i.e. 0.5 mg to 8 mg BID), with the plasma concentrations of risperidone and 9-hydroxyrisperidone increasing proportionately with dose. The median trough concentration of risperidone increases by 0.46 μg/L for each mg dose per day (r=0.97) and that of the active moiety by 6.6 μg/L for each mg dose per day. In EM subjects, 10% of the drug-derived material in plasma is risperidone and 70% is its 9-hydroxy metabolite. In contrast, in PM subjects 71% of the material in plasma is risperidone and 9-hydroxyrisperidone is barely detectable.

Distribution

Both risperidone and 9-hydroxyrisperidone are rapidly and extensively distributed throughout the body. The distribution half-life is 6 minutes. Both risperidone and 9-hydroxyrisperidone are bound to plasma proteins, 85 and 77% respectively. The compounds do not affect each other's binding, which is constant over a wide range of concentrations. The binding of risperidone to α1-acid glycoprotein (85%) and albumin (83%) is similar. The blood/plasma concentration ratio is 0.67. The plasma protein binding is not affected by warfarin, phenytoin or sulfamethazine. The volume of distribution of risperidone at steady state (Vss) is 87L (1.2L/kg).

Metabolism

Risperidone is extensively metabolised. The major metabolite, 9-hydroxyrisperidone, has a pharmacological profile similar to that of the parent drug, so that the pharmacologically active moiety is risperidone and 9-hydroxyrisperidone. The 9-hydroxylation of risperidone is catalysed by CYP2D6 and hence is subject to the same genetic polymorphism as the 4-hydroxylation of debrisoquin. Individuals can be phenotyped extensive (EM) or poor (PM) metabolisers of risperidone and there is an almost eightfold difference in the total plasma clearance of the drug between the phenotypes. Approximately 8% of the Caucasian population are PM. There are far fewer PM subjects among individuals of Eastern origin. The bioavailability of risperidone in EM subjects after oral administration is 66% as a result of pre-systemic metabolism, while the absolute bioavailability of the active moiety (risperidone plus 9-hydroxyrisperidone) is 108%. In PM subjects the absolute bioavailability is 82%. As PM subjects produce very little 9-hydroxyrisperidone, the absolute bioavailability of the active moiety (mean 75%, range 70-80%) is similar to that of the parent compound in such individuals. Although plasma concentrations of risperidone differ considerably between EM and PM subjects, concentrations of the active moiety do not. The plasma AUC of risperidone differs sevenfold between EM and PM subjects, while the AUC of the active moiety differs by only twofold. Following intramuscular administration the absolute bioavailability of risperidone is 105%, while that of the active moiety is 107%.

The other significant route of metabolism is oxidative N-dealkylation, which is not subject to genetic polymorphism. Acid metabolites formed by this reaction and 9-hydroxylation account for 10-13% of the dose. A small amount of the drug is subject to 7-hydroxylation, which accounts for 1% of the dose in PM subjects and 5% in EMs. Hence this pathway appears also to be catalysed by CYP2D6 and subject to genetic polymorphism. A further 3-5% of the dose is excreted in the urine as glucuronide conjugates.

Elimination

The elimination of risperidone from the plasma following intravenous administration is best described by a two-compartment open model with first order elimination. Elimination of risperidone from the plasma is rapid, with a half-life of 2-4 hours (mean 2.8 hours) in EM subjects. The half-life in PM subjects is longer, 17-22 hours. Elimination of its 9-hydroxymetabolite is much slower, with a half-life of 20-24 hours. Elimination of the active moiety is independent of phenotype, with a half-life of approximately 20 hours. This represents largely 9-hydroxyrisperidone in EM subjects and risperidone in PM subjects. Studies with doses of 4 mg risperidone indicate that there may be a slower elimination phase, with a half-life of 10-15 hours in EM subjects. However, as this accounts for only 11% of the AUC, it is of little significance.

The major route of elimination of risperidone is by hepatic metabolism, although the predominant pathway differs in EM and PM subjects. The major excretory route is urinary, 70% of the dose being accounted for in this way. A further 14% of the dose is excreted in the faeces. The primary route of excretion of the active metabolite is also in the urine. In EM subjects 3.5% of the dose is excreted unchanged in the urine in 7 days, while in PM subjects this route of elimination accounts for 30% of the dose. The renal clearance of risperidone is only approximately 12 mL/min and does not vary with phenotype. Hence this route of elimination represents only 3% of total plasma clearance (394 mL/min) in EM subjects, but approximately 20% of total plasma clearance (54 mL/min) in PM subjects.

There are no differences between Japanese and Caucasian subjects in the pharmacokinetics of risperidone or the formation of its active metabolite, although the frequency of the PM phenotype is lower in the former group.

Placental transfer of risperidone and its metabolite is very low in rats. There is evidence from studies in animals that levels of risperidone and 9-hydroxyrisperidone in breast milk equal or exceed those in plasma. It is estimated, based on the pH-partition hypothesis, that 0.25% of a maternal dose of risperidone would be excreted into breast milk, resulting in a dose to a nursing infant of 5% of that of the mother. However, specific human information is not available.

Pharmacokinetics in children have not been studied. The elimination half-life of the active moiety of risperidone is significantly higher and the renal clearance is lower in the elderly than in young adults. The elimination half-life of 9-hydroxyrisperidone is longer in subjects with renal insufficiency and in liver disease the fraction of risperidone is increased.

IV.3 Pharmacodynamics

Risperidone is an antipsychotic agent used to treat schizophrenia and other psychotic conditions including acute mania, serious behavioural disturbance in patients with dementia, conduct and other disruptive behaviour disorders. It is a benzisoxazole derivative, chemically unrelated to any currently available antipsychotic drug. Risperidone was first marketed in the US and the UK in 1993 and is now widely available throughout the world

The antipsychotic effect of risperidone is thought to be related to its ability to block dopamine DA) D2 receptors and serotonin (5-HT2) receptors. Its affinity for 5-HT2 receptors is greater than its affinity for D2 receptors. Rodent studies demonstrate that risperidone is an effective 5-HT2 antagonist in vivo and antagonises the stimulating effect of lysergic acid diethylamide (LSD) at low doses. At higher doses risperidone can block the effect of direct and indirect DA agonists to stimulate D2 receptors. Based upon in vivo binding data, risperidone, at clinically effective doses, should produce weak blockade of limbic and striatal D2 receptors and potent blockade of 5-HT2 receptors in humans. In dog studies risperidone shows potent D2 antagonistic properties with a relatively long duration of action (24 hours at 4 times the lowest ED50). In rat studies D2 antagonism is comparable to that of haloperidol but some CNS-controlled functions, such as the induction of catalepsy, are relatively much less affected by risperidone.

In whole animal studies risperidone caused a reduction in spontaneous and amphetamine-induced motor activity. The drug had antiemetic activity and it enhanced prolactin release. Risperidone also caused amphetamine-challenged rats to display marked behavioural disinhibitory effects.

Risperidone is also a potent α1-adrenergic antagonist and histamine H1 antagonist. In whole animal studies risperidone reverses the antidiarrhoeal action of clonidine and protects against norepinephrine-induced lethality. Risperidone also antagonised the peripheral effects of histamine. Risperidone has low affinity for the 5-HT1A, 5-HT1B/1C/1D, D1, D3, D4, and β-adrenergic, muscarinic, cholinergic, benzodiazepine and μ-opiate receptors.

The pharmacodynamic effects of the major metabolite, 9-hydroxyrisperidone, are very similar to those of risperidone itself. In doses of 4-8 mg daily risperidone appears to be an effective antipsychotic drug, decreasing delusions, hallucinations and disorganisation while producing fewer parkinsonian side effects than haloperidol at doses of 10-20 mg daily or higher. Effects of risperidone in humans include insomnia, agitation, anxiety, blurred vision, dry mouth, rhinitis, sedation, diminished male potency and postural dizziness. These effects are relatively mild. There is no evidence that it produces cardiovascular or ECG abnormalities, other than a slight increase in heart rate, or that it lowers the seizure threshold. It appears to cause weight gain. Risperidone increases plasma prolactin levels in humans and the increase is likely to be prolonged.

Risperidone produces extrapyramidal symptoms (EPS) in a dose-dependent manner. Less antiparkinsonian medication is required to minimise EPS in risperidone-treated compared with haloperidol-treated patients. There is limited information about the risk of tardive dyskinesia associated with risperidone usage. The effects of risperidone in humans appear to be caused by its active metabolite 9-hydroxyrisperidone.

IV.4 Clinical efficacy

Main studies performed in healthy volunteers and clinical experience
The clinical efficacy of risperidone is reviewed in several publications and many clinical trials. These publications are summarised below.

Efficacy in Adults

Schizophrenia
Positive, negative and disorganisation (incoherence, inappropriate affect, loose associations, poverty of thought content) symptoms in acute and chronic schizophrenia can be treated with risperidone. The efficacy of risperidone in the treatment of schizophrenia was established in several open and double-blind studies. Efficacy over the dose range 1-16 mg daily was established in acute schizophrenia, with a dose response which plateaued at 6 mg daily. Most patients benefited from doses of 4-6 mg daily given in once daily or two divided doses. Extrapyramidal symptoms were more likely with doses above 10 mg daily. Improvement of symptoms and a significant reduction in relapse rate of patients with schizophrenia was demonstrated with risperidone treatment. In comparison with conventional antipsychotic treatment, risperidone was equal or superior in efficacy and in conventional treatment-resistant schizophrenia a beneficial effect with risperidone was observed.

Efficacy in children has not been studied. Treatment in the elderly should be initiated at a dose of 0.5 mg twice daily increasing to 2 mg twice daily as required. Treatment in patients with renal insufficiency and in liver disease should be initiated at a dose of 0.5 mg twice daily, which may be increased in steps of 0.5 mg twice daily to a dose of 1-2 mg twice daily.

When switching from other antipsychotic medication to risperidone, gradual discontinuation of previous treatment while initiating risperidone is recommended to avoid withdrawal effects.

Bipolar Mania
Risperidone is effective in the treatment of acute manic episodes using an initial dose of 2-3 mg once daily by mouth. Dose adjustments of 1 mg daily may be made at intervals of not less than 24 hours up to a total of 6 mg daily. In short term studies in acute bipolar mania the addition of risperidone to mood stabilisers such as lithium or valproate resulted in significant improvement in symptoms. Open label studies suggest that atypical antipsychotics such as risperidone, may have long term mood-stabilising effects. The initial dosage regime in the elderly or patients with renal or liver disease should be reduced as for schizophrenia.

Behavioural Disturbances in Patients with Dementia
Risperidone treatment is effective in the treatment of the non-cognitive symptoms of dementia, such as verbal and physical aggression, agitation, sleep disturbances and wandering. In a small clinical trial 60 demented patients were randomised to risperidone 1mg daily (increasing to 2 mg daily if there was no response after 4 weeks), olanzapine 5mg/day (10 mg/day) or promazine 50 mg/day (100 mg/day). At the end of the 8th week a global improvement was obtained in 80% of patients treated with risperidone or olanzapine and in 65% on promazine. Pooled data from three randomised, placebo-controlled trials examined the efficacy and safety of risperidone for the treatment of agitation, aggression and psychosis associated with dementia. 1150 patients with all forms of dementia were included and the mean dose of risperidone at end point was 1 mg/day. There was a significantly greater improvement in Cohen-Mansfield agitation inventory score, behavioural pathology in Alzheimer's disease score and psychotic symptoms score with risperidone compared with placebo. Clinical global impression scores were also significantly higher with risperidone treatment.

Efficacy in Children and Adolescents

Conduct and Other Disruptive Behaviour Disorders
Aggression and disruptive behaviour, symptoms of many psychiatric disorders including attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder, mental retardation, pervasive development disorders, intermittent explosive disorder and personality disorder, have been treated effectively with risperidone. Early case reports indicated therapeutic response in children aged 5 to 16 years with aggressive and violent behaviour treated with risperidone 0.75-2.5 mg daily. A retrospective review of 51 children and adolescents with severe behavioural disturbances demonstrated clinical improvement in 76% over 9 months with risperidone treatment. A larger retrospective review of 106 children with a variety of conduct and disruptive behaviour disorders demonstrated long term treatment with risperidone (0.25- 8.0 mg/day, mean duration of treatment, 11 months) resulted in clinical global improvement in 85% of patients at the final study visit. Most children were taking concurrent psychiatric medications.

IV.5 Clinical safety

IV.5.1.1 Introduction
The innovator product Risperdal® is widely available on the European market and the safety profile of risperidone in adults and children has been well documented in published literature. The proposed contraindications, precautions and warnings applied to this formulation of risperidone are the same as those applied to the reference product Risperdal® (Janssen-Cilag) and are supported by the findings in the published literature. The safety of risperidone has been reviewed in several publications. These data are presented in the following sections.

IV.5.1.2 Patient exposure
Not applicable, as the application is a ‘generic application’.

IV.5.1.3 Adverse events
The most common adverse effects with risperidone include insomnia (11%), anxiety (5%) and agitation (7%), dizziness (2%) and rhinitis (3%). Headache, dyspepsia, nausea, abdominal pain, constipation, blurred vision, sexual dysfunction including priapism, urinary incontinence, dysphagia, sialorrhoea, rash and other allergic reactions, drowsiness, concentration difficulties and fatigue have been reported less commonly. Menstrual disturbances have been reported in 15% of Japanese female patients. Orthostatic hypotension and hypertension have both been reported infrequently. Other adverse effects with risperidone include cerebrovascular accidents, tachycardia, weight gain, oedema, somnolence, increased liver enzyme values and mild decreases in neutrophil and thrombocyte counts. There has been one report of cholesatasis in a patients who had been taking risperidone for 8 years. Risperidone may cause dose-dependent increases in prolactin levels. In almost all cases this was not associated with a change in symptoms or with adverse effects. In rare cases hyperglycaemia, worsening of diabetes mellitus and the development of ketoacidosis have been reported. Other rare effects include seizures, body temperature dysregulation, neuroleptic malignant syndrome, extrapyramidal reactions including acute dystonias and parkinsonism and tardive dyskinesia.

There have been three reports of death associated with therapeutic doses of risperidone. The one case, in which the patient was taking only risperidone no serum levels were provided. One case was associated with prolongation of the QTc interval and the patient experienced a cardiac arrest. The patient had also been taking haloperidol and amantadine. The third case was a patient who developed neuroleptic malignant syndrome, seizures, renal failure and circulatory collapse. He was on venlafaxine and benzotropine as well as risperidone 1 mg twice daily.

The development of tardive dyskinesia or neuroleptic malignant syndrome should result in the discontinuation of risperidone. Gradual withdrawal of risperidone is recommended because of the risk of withdrawal symptoms (including nausea, vomiting, sweating and insomnia) with abrupt cessation. Recurrence of psychotic symptoms may also occur and the emergence of involuntary movement disorders (such as dyskinesia) has been reported.

In children the most frequently reported adverse effects in short-term studies were weight gain, increased appetite, fatigue, drowsiness, dizziness and drooling. Anticholinergic and extrapyramidal effects have been reported. The development of depressive symptoms in children without previous mood disorders occurred rarely with risperidone treatment. Elevated prolactin levels have been observed in children aged 5 to 15 years old after 24 weeks of treatment and these were not associated with adverse effects. In long-term studies of up to 6 months treatment duration adverse effects included sedation, increased appetite and weight gain. In one study 2 of 13 children treated long-term developed mild reversible withdrawal dyskinesias when risperidone was discontinued. A case report describes 2

children who developed hyperammonaemia with frank manic behaviour while taking both valproic acid and risperidone and there has been one case report of priapism in a 12 year old boy treated with risperidone.

IV.5.1.4 Safety in special populations

Pregnancy and Nursing Mothers

The safety of risperidone in pregnancy has not been fully established. A review of risperidone exposure during pregnancy in humans showed no increased risk of spontaneous abortions, structural malformations or foetal teratogenicity with treatment. However, risperidone should only be used during pregnancy if the benefits outweigh the risks. Both risperidone and 9-hydroxyrisperidone appear in breast milk of dogs in concentrations equal to or higher than plasma levels. Women receiving risperidone should not breast feed.

Children

Risperidone may be used in children at a starting dose of 0.25 mg or 0.5 mg increasing in increments of 0.25 mg and 0.5 mg respectively until there is a therapeutic response.

Elderly

The elimination half-life of the active moiety of risperidone is significantly higher and the renal clearance lower in the elderly than in young adults. Treatment should be initiated at a dose of 0.5 mg twice daily. Following analysis of data from controlled trials there was evidence that the use of risperidone in elderly patients with dementia appeared to be associated with an increased risk of cerebrovascular adverse effects such as stroke and transient ischaemic attacks. In 4 studies involving 764 such patients treated with risperidone there were 29 cases of cerebrovascular events, 4 fatal, versus 7 cases (1 fatal) in 466 patients given placebo. Postmarketing data for elderly dementia patients, representing over 2.4 million patient-years of exposure, included 37 cases, of which 16 were fatal. In a more recent review of data in the elderly increased mortality was observed for all antipsychotic medications, which was greater for haloperidol compared with risperidone and in a double blind trial in 1721 patients with dementia no difference in mortality was observed between risperidone and placebo. It is therefore recommended that the risk of cerebrovascular events should be considered in the treatment of patients with a history of stroke or transient ischaemic attack or other risk factors for cerebrovascular disease including hypertension, diabetes, smoking or atrial fibrillation.

Patients with Renal Disease / Patients with Hepatic Disease

The elimination half-life of 9-hydroxyrisperidone is longer in subjects with renal insufficiency and in liver disease the fraction of risperidone is increased. Treatment should be initiated at a dose of 0.5 mg twice daily, which may be increased in steps of 0.5 mg twice daily to a dose of 1-2 mg twice daily.

IV.5.1.5 Safety related to drug-drug interactions and other interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by risperidone. Risperidone may also enhance the effects of antihypertensives. There may an increased risk of QT prolongation when risperidone is given with other drugs that are known to cause this effect. The anticholinergic effects of risperidone may be increased by other drugs with anticholinergic properties. Risperidone may antagonise the actions of levodopa and other dopaminergics.

Carbamezepine has been shown to decrease the antipsychotic fraction (risperidone plus 9-hydroxyrisperidone) of risperidone and a similar effect may be seen with other enzyme inducers. Phenothiazines, tricyclic antidepressants and some beta blockers may increase the plasma concentrations of risperidone but not those of the antipsychotic fraction. Fluoxetine, paroxetine, haloperidol and CYP2D6 inhibitors may increase the plasma concentration of risperidone but less so the active antipsychotic fraction. Dose adjustment of risperidone may be necessary in such situations.

Cimetidine and ranitidine increase the bioavailability of risperidone but only marginally that of the active psychotic fraction. The anticholinergic effects of risperidone may be increased by other drugs with anticholinergic properties and postural hypotension may be exaggerated by the combination of risperidone with other hypotensive drugs. The concomitant use of risperidone with amitriptylline, erythromycin, galantamine, donepezil, valproate or lithium showed no clinically relevant effects of the pharmacokinetics of risperidone or the active antipsychotic fraction or on the pharmacokinetics of the concomitant medication.

IV.5.1.6 Overdosage

Overdose with risperidone may result in somnolence, muscular rigidity, hypotension and lethargy. Other features may

include tachycardia, hypertension, increased QTc interval, convulsions and dystonic reactions. There have been three reported deaths following overdose with risperidone, two with no plasma levels available, and one with a plasma level of 1800 µg/L, 500-fold greater than the normal therapeutic range. There have been several cases of fatal overdose associated with risperidone taken with other drugs. Most of these were intentional suicides. Treatment of overdose is symptomatic and supportive, including cardiovascular monitoring, plasma expansion, gastric lavage and activated charcoal where indicated.

IV. 6 Discussion on the clinical aspects

Risperidone solution 1 mg/ml was developed to have pharmaceutical qualities as close as possible to Risperdal® solution 1 mg/ml (Janssen-Cilag). Risperidone solution is an aqueous oral solution at time of administration and contains an active substance (risperidone) in the same concentration (1 mg/ml) as Risperdal® solution which is currently approved as a medicinal product. The excipients used in the Applicant's product vs. the reference product are almost identical, the only qualitative difference being the use of a hydrochloric acid for pH adjustment versus the use of sodium hydroxide. This minor difference in excipients is not considered significant. Therefore a similar benefit/risk profile to Risperdal® solution is expected.

Risperidone is widely available on the European market and its clinical pharmacology in adults and children has been well documented in published literature. The overview on the clinical pharmacology presented in support of the current application is well-referenced and is adequate.

Risperidone was first marketed in the US and the UK in 1993 and is now widely available throughout the world. Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions in which positive, negative and disorganisation (inappropriate affect, loose associations, poverty of thought content) symptoms are present. It is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. Risperidone's clinical efficacy is established for the indications sought through large numbers of clinical studies and extensive global clinical experience. The Applicant has supplied a comprehensive and extensive list of literature references that supports this marketing authorization application. The overview of clinical efficacy is adequate.

The most common adverse effects with risperidone include insomnia, anxiety and agitation, dizziness and rhinitis. Other serious but rare effects include seizures, body temperature dysregulation, neuroleptic malignant syndrome and tardive dyskinesia. Deaths are rare with risperidone and may be associated with prolonged QTc interval. Possible interactions of risperidone with other drugs have not been systematically evaluated. Hypotension, anticholinergic effects and CNS effects may be enhanced when risperidone is given with other drugs producing such effects. Dose adjustments may be necessary when risperidone is given with drugs which increase or decrease the plasma levels. Risperidone is contraindicated in lactating women. It should be given in reduced doses to patients with renal or liver insufficiency and in the elderly. The risk of cerebrovascular events should be considered in the treatment of patients with a history of stroke or transient ischaemic attack or other risk factors for cerebrovascular disease.

The optimal dose ranges and dose regimens for risperidone have been well established. As discussed earlier, certain sub-populations have been defined as high-risk patients with regard to their susceptibility to risperidone-related adverse effects. Due consideration is given to these patient groups in the proposed prescribing information.

Known and potential interactions are well documented and are included in the proposed prescribing information. The potential to interfere with activities requiring mental alertness may adversely affect ability to drive or to operate machinery, and these effects are taken into account in the proposed prescribing information.

In conclusion, there is a vast amount of accumulated experience with the use of risperidone since it was first introduced into clinical practice. Its safety profile is well established and no new or different safety issues have been identified in the course of this review.

V OVERALL CONCLUSIONS

The proposed formulation of Risperidone solution 1 mg/mL, is essentially similar to Risperdal® solution 1 mg/mL, based on the pharmaceutical data and the findings in the literature and is suitable for the proposed indications. The

risk/benefit ratio of the proposed formulation is expected to be that of Risperdal® solution. With regard to the clinical aspects no potentially serious risks to public health has been identified. Given issues have neither been identified with the innovator product nor with this generic product in comparison to the innovator, a Risk Management Plan is not required.

The proposed SmPC reflects the safety and efficacy profile of the brand leader Risperdal® solution. The Applicant harmonised the product information according to the final outcome of the Article 30 referral for the innovator product Risperdal®.

The Applicant has submitted an appropriate User Test conducted by Magmapharma in February 2007 that meets the legal requirements of EU legislation Article 59 (3) and 61 (1) of Directive 2001/83 as amended by Directive 2004/27/EC. The criterion for a successful test was fulfilled (≥ 90%) and therefore the test is deemed successful.

Risperidone has a well-recognised efficacy and an acceptable level of safety in the indications approved for Risperdal, and corresponding products have been widely used in many countries. Therefore, the submission of PSURs every 3 years is supported.

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country

The procedure concluded successfully with Day 90 being 11th February 2009.

VI REVISION DATE

February 2009