Public Assessment Report

Decentralised Procedure

Risperidone 1mg/ml Oral Solution

Procedure No: UK/H/5601/001/DC

UK Licence No: PL 00427/0239

Rosemont Pharmaceuticals Limited
LAY SUMMARY

Risperidone 1mg/ml Oral Solution

This is a summary of the Public Assessment Report (PAR) for Risperidone 1mg/ml Oral Solution (PL 00427/0239; UK/H/5601/001/DC). It explains how the application for Risperidone 1mg/ml Oral Solution was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Risperidone 1mg/ml Oral Solution.

For practical information about using Risperidone 1mg/ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Risperidone Oral Solution’ in this report.

What is Risperidone Oral Solution and what is it used for?
Risperidone Oral Solution is a generic medicine. This means that Risperidone Oral Solution is similar to a ‘reference medicine’ already authorised in the UK called Risperdal 1 mg/ml Oral solution (Janssen-Cilag Limited), which was authorised on 21 November 1995.

Risperidone belongs to a group of medicines called ‘anti-psychotics’ and is used to treat the following:

- Schizophrenia, where the patient may see, hear or feel things that are not there, believe things that are not true or feel unusually suspicious, or confused.
- Mania, where the patient may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called “bipolar disorder”.
- Short-term treatment (up to 6 weeks) of long-term aggression in people with Alzheimer’s dementia, who harm themselves or others. Alternative (non-drug) treatments should have been used previously.
- Short-term treatment (up to 6 weeks) of long-term aggression in intellectually disabled children (at least 5 years of age) and adolescents with conduct disorder.

Risperidone Oral Solution can help alleviate the symptoms of the above diseases and stop the symptoms from coming back.

How does Risperidone Oral Solution work?
Risperidone Oral Solution contains the active ingredient risperidone, which acts on the brain to help alleviate the symptoms of the indicated diseases and stop the symptoms from coming back.

How is Risperidone Oral Solution used?
Risperidone Oral Solution is swallowed in a drink of water or orange juice.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Risperidone Oral Solution can only be obtained with a prescription.

What benefits of Risperidone Oral Solution have been shown in studies?
No additional studies were needed as Risperidone Oral Solution is a generic medicine that is an oral solution and contains the same active substance as the reference medicine, Risperdal 1 mg/ml Oral solution (Janssen-Cilag Limited, UK).
In addition, the Marketing Authorisation Holder (Rosemont Pharmaceutical Limited) has provided data from the published literature on risperidone.

**What are the possible side effects of Risperidone Oral Solution?**

Because Risperidone Oral Solution is a generic medicine and is bioequivalent to the reference medicine Risperdal 1 mg/ml Oral solution (Janssen-Cilag Limited), the benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Risperidone Oral Solution, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why is Risperidone Oral Solution approved?**

It was concluded that, in accordance with EU requirements, Risperidone Oral Solution has been shown to have comparable quality and to be comparable to Risperdal 1 mg/ml Oral solution (Janssen-Cilag Limited, UK). Therefore, the MHRA decided that, as for Risperdal 1 mg/ml Oral solution (Janssen-Cilag Limited, UK), the benefits outweigh the identified risks and recommended that Risperidone Oral solution can be approved for use.

**What measures are being taken to ensure the safe and effective use of Risperidone Oral Solution?**

A risk management plan has been developed to ensure that Risperidone Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Risperidone Oral Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

**Other information about Risperidone Oral Solution**

Germany, France and the UK agreed to grant a Marketing Authorisation for Risperidone Oral Solution on 15 December 2014. A Marketing Authorisation was granted in the UK on 09 January 2015.

The full PAR for Risperidone 1 mg/ml Oral Solution follows this summary.

For more information about treatment with Risperidone 1 mg/ml Oral Solution read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2015.
TABLE OF CONTENTS

I Introduction .............................................. Page 5
II Quality aspects ......................................... Page 6
III Non-clinical aspects .................................. Page 11
IV Clinical aspects ........................................ Page 12
V User consultation ....................................... Page 14
VI Overall conclusion, benefit/risk assessment and recommendation .......................... Page 14

Annex 1 - Table of content of the PAR update for MRP and DCP .................................. Page 15
Scientific discussion

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Risperidone 1mg/ml Oral Solution (PL 00427/0239; UK/H/5601/001/DC) could be approved. This is a prescription-only medicine (POM), which is indicated for the:

• treatment of schizophrenia;
• treatment of moderate to severe manic episodes associated with bipolar disorders;
• 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;
• 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.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany and France as Concerned Member State (CMS). The application for Risperidone 1 mg/ml Oral Solution was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. Risperidone 1 mg/ml Oral Solution cross-refers to the reference medicinal product Risperdal 1 mg/ml Oral solution (Janssen-Cilag Limited, UK), which was authorised in the UK as a hybrid application, cross-referring to the reference product Risperdal 4 mg tablets (PL 00242/0189, Janssen-Cilag Limited, UK). Risperdal 4 mg tablets were authorised as a new active substance (full dossier) via a UK national procedure on 8 December 1992.

Risperidone 1mg/ml Oral Solution contains the active ingredient, risperidone. Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics.

There is no paediatric development programme, and none is considered necessary.

No new non-clinical or clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years. A bioequivalence study was not necessary to support this application for an oral solution.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 15 December 2014. After a subsequent national phase, a licence was granted in the UK on 09 January 2015.
II QUALITY ASPECTS

II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Each millilitre of Risperidone 1mg/ml Oral Solution contains 1 milligram of risperidone. The product is a clear colourless solution.

The product also contains the pharmaceutical excipients sodium benzoate (E211), tartaric acid, sodium hydroxide and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in amber (Type III glass) bottles, with high density polyethylene (HDPE), expanded polyethylene (EPE) wadded, child resistant closures. The product is also packaged with:
1. a syringe with a polypropylene (PP) body and purple plunger with a capacity of 3ml (equivalent to 3mg) and dosing graduations at every 0.25ml (equivalent to 0.25mg)
2. bottle adaptor, with a low-density polyethylene (LDPE) press – in adaptor.

The product is available in a bottle containing 100 ml of oral solution.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff. A Certificate of Conformity has been provided that confirms compliance with ISO 8317 (Child resistant packaging requirements) and BS EN 28317 (The Medicines (Child Safety) Regulations 2003).

II.2 DRUG SUBSTANCE
Risperidone
INN: Risperidone
Chemical Name: 3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one
Molecular Formula: C_{23}H_{27}FN_{4}O_{2}
Structure

Molecular weight: 410.5
Appearance: White or almost white powder.
Solubility: Practically insoluble in water, freely soluble in methylene chloride and sparingly soluble in ethanol (96 percent). It dissolves in dilute acids solutions.

Risperidone is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance risperidone, except for stability data is covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability or by information provided by the Applicant and the relevant active substance supplier.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable, oral solution bioequivalent to the reference medicinal product Risperdal 1 mg/ml Oral Solution (Janssen-Cilag Limited). Suitable pharmaceutical development data have been provided for this application.

All the excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months for the unopened product and 3 months for the opened product, with the special storage conditions ‘Do not freeze’, has been accepted.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this application for this aqueous oral solution product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for the application for Risperidone 1mg/ml Oral Solution.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the
MHRA website. The current labelling is presented below:
III   NON-CLINICAL ASPECTS

III.1   Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of risperidone are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2   Pharmacology
Not applicable, see Section III.1 Introduction, above.

III.3   Pharmacokinetics
Not applicable, see Section III.1 Introduction, above.
III.4 Toxicology
Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental exposure to risperidone is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Risperidone 1mg/ml Oral Solution, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction.
The clinical pharmacology of risperidone is well-known. No new clinical pharmacology data have been submitted and none are required for this type of application. According to CPMP guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **), bioequivalence studies may be waived if a test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as the reference medicine, an approved oral solution. This is the case for Risperidone 1mg/ml Oral Solution. The excipient profile is not expected to affect pharmacokinetic profile of the active substance.

IV.2 Pharmacokinetics
The pharmacokinetic properties of risperidone are well known and are adequately described in the applicant’s non-clinical overview. No new pharmacokinetic data were submitted and none are required for an application of this type.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of risperidone are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy
The clinical efficacy of risperidone is well-known. No new efficacy data are presented or are required for this type of application.

IV.5 Clinical Safety
No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Risperidone 1 mg/ml Oral Solution.

A summary of safety concerns is listed in the table below:
### Summary of safety concerns

#### Important identified risks
- Hypersensitivity to Risperidone or to any of the excipients in the Rosemont formulation.
- Increased mortality in elderly people with dementia and concomitant use of Furosemide.
- Increased risk of cerebrovascular adverse events.
- Increased risk of orthostatic hypotension.
- Increased risk of leukopenia, neutropenia and agranulocytosis especially in patients with a history of clinically low white blood cell count or a drug-induced leukopenia / neutropenia.
- Tardive dyskinesia / extrapyramidal symptoms.
- Neuroleptic malignant syndrome.
- Risk Parkinson’s disease may worsen.
- Risk of hyperglycaemia, diabetes mellitus and exacerbation of pre-existing diabetes.
- Risk of significant weight gain.
- Risk of hyperprolactinaemia.
- QT prolongation.
- Seizures.
- Risk of priapism.
- Risk of disruption in body temperature regulation.
- Renal and hepatic impairment.
- Risk of venous thromboembolism.
- Intraoperative Floppy Iris Syndrome.
- Sedative effect in paediatric population.
- Risk of rhabdomyolysis

#### Important potential risks
- Medication error due to measuring incorrect volume resulting in incorrect dosage
- Off label use
- Carcinogenicity (pituitary adenomas,

### Summary of safety concerns

<table>
<thead>
<tr>
<th>Missing information</th>
<th>endocrine pancreas tumours, breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cognitive and motor impairment</td>
</tr>
<tr>
<td></td>
<td>Suicidality</td>
</tr>
<tr>
<td></td>
<td>Depression in patients with affective disorders</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal obstruction</td>
</tr>
<tr>
<td></td>
<td>Decreased bone mineral density/osteoporosis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnancy and lactation</td>
</tr>
</tbody>
</table>
Routine Pharmacovigilance and routine risk minimisation are proposed for all safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Risperidone 1 mg/ml Oral Solution.

V. USER CONSULTATION
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the PILs for Risperdal 1mg/ml oral solution (Janssen-Cilag Limited, UK), which has been harmonised by the Committee for Medicinal Products for Human use, CHMP) and the applicant’s own user-tested’ and approved Clobazam 2mg/ml Oral Suspension. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
QUALITY
The important quality characteristics of Risperidone 1mg/ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of risperidone are well-known, no additional data were required.

EFFICACY
No new efficacy data have been submitted and none are required for this type of application.

SAFETY
No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with risperidone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
Annex 1 - Table of content of the PAR update for MRP and DCP
Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y/N (version)</td>
</tr>
</tbody>
</table>