Public Assessment Report

Risperdal Quicklet 3mg Orodispersible Tablets
Risperdal Quicklet 4mg Orodispersible Tablets

Risperidone

PL 00242/0407
PL 00242/0408

Janssen-Cilag Limited

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific Discussion</td>
<td>3</td>
</tr>
<tr>
<td>Overall Conclusion And Risk Benefit/Analysis</td>
<td>14</td>
</tr>
<tr>
<td>Steps Taken During Assessment</td>
<td>15</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>16</td>
</tr>
<tr>
<td>Labels and Leaflet</td>
<td>38</td>
</tr>
</tbody>
</table>
Lay Summary

The MHRA granted a National Marketing Authorisation (licence) to Janssen-Cilag Limited for the medicinal products Risperdal Quicklet 3mg and 4mg Orodispersible Tablets on 7th December 2006.

Risperdal Quicklet 3mg and 4mg Orodispersible Tablets contain the active ingredient risperidone. Risperidone is a novel anti-psychotic drug indicated for use in the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive and/or negative symptoms are prominent.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Risperdal Quicklet 3mg and 4mg Orodispersible Tablets outweigh the risks, hence a Marketing Authorisation has been granted.
SCIENTIFIC DISCUSSION

Introduction

This Public Assessment report is based on the assessment reports for two national abridged standard applications for Risperdal® Quicklet® 3mg and 4mg tablets. The applications were made under EC article 10.1(a)(iii), last paragraph. The applications for orodispersible tablets are made as a line extension to Janssen’s existing marketing authorisations for Risperdal Quicklet 0.5mg, 1mg and 2mg orodispersible tablets (PL 00242/0378-0380, granted 7th January 2003). As a result no clinical or preclinical data, apart from the bioequivalence study, were submitted with the applications.

Risperidone is a novel anti-psychotic drug indicated for use in the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive and/or negative symptoms are prominent. Risperidone is a prescription only medicine.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

The applicant has a Ph. Eur. certificate of suitability for the active risperidone and a copy of this certificate has been provided. There is a declaration of access from the active manufacturer authorising the applicants to use the certificate of suitability for their applications. As there is a certificate of suitability for the active in support of this application, no further assessment of the manufacture of the drug substance is required.

The drug substance specification was amended during assessment and is now satisfactory. Results from analysis of three batches of the active demonstrated compliance with the Ph. Eur. monograph.

Container Closure System

The drug substance is stored in polythene bags and data from three batches have been provided. Confirmation was provided that the bags meet Ph. Eur and EU requirements for plastics.

Stability

Satisfactory stability data for up to 36 months real-time storage was provided. Confirmation was given that all impurities in the Ph. Eur. monograph were tested for.
DRUG PRODUCT

Pharmaceutical Development
The product was developed to provide a formulation which was orodispersible and palatable.

Manufacture
The 3mg tablet strength is described as coral, square, biconvex, printed “R3”. The 4mg tablet strength is described as coral, square, biconvex, printed “R4”. The qualitative composition of both strengths is given below and both are a direct scale-up / scale-down versions of each other.

The source of risperidone is the same as all other approved risperdal formulations for the Market Authorisation Holder. Brief descriptions were provided for the function of each of the excipients in the proposed formulation and this is considered satisfactory. Satisfactory description of the manufacturing process was provided.

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation No.</strong></td>
<td><strong>Function</strong></td>
<td><strong>Standard</strong></td>
</tr>
<tr>
<td>Risperidone</td>
<td>Drug Substance</td>
<td>EU (Ph. Eur.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US (DMF11438)</td>
</tr>
<tr>
<td>Polacrilex Resin</td>
<td>Taste masking agent</td>
<td>US (DMF 12903)</td>
</tr>
<tr>
<td>Gelatin Type A</td>
<td>Primary structural agent</td>
<td>Ph. Eur. / NF</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Structural agent</td>
<td>Ph. Eur. / USP</td>
</tr>
<tr>
<td>Glycine</td>
<td>Mouth feel enhancer &amp; structural agent</td>
<td>Ph. Eur. / USP</td>
</tr>
<tr>
<td>Simethicone</td>
<td>Defoaming agent</td>
<td>Ph. Eur. / USP</td>
</tr>
<tr>
<td>Carbomer 934P</td>
<td>Viscosity imparting agent</td>
<td>Ph. Eur. / NF</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>Neutralising agent</td>
<td>Ph. Eur. / NF</td>
</tr>
<tr>
<td>Aspartame</td>
<td>Flavour, sweetener</td>
<td>Ph. Eur. / NF</td>
</tr>
<tr>
<td>Ferric Oxide</td>
<td>Colorant</td>
<td>NF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EU directive 78/25 – E172</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EU directive 95/45</td>
</tr>
<tr>
<td>Xanthan Gum</td>
<td>Viscosity imparting agent</td>
<td>Ph. Eur. / NF</td>
</tr>
<tr>
<td>Peppermint Oil</td>
<td>Flavourant</td>
<td>Ph. Eur. / NF</td>
</tr>
<tr>
<td>Purified Water</td>
<td>Diluent</td>
<td>Ph. Eur. / USP</td>
</tr>
<tr>
<td>Total Tablet Weight</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Process validation and evaluation
Satisfactory batch data was provided for both strengths of Risperdal Quicklet.

Control of Excipients
Gelatin (Type A), mannitol, glycine, simethicone, carbomer 934P, sodium hydroxide, aspartame, peppermint oil, xanthan gum and purified water are all controlled by their Ph. Eur. monographs. Typical certificates of analysis are provided from the manufacturer of the finished product for each of the excipients. Satisfactory BSE/TSE risk certificates were provided for all excipients.

Amberlite IRP64 is the proprietary name for polacrilex resin, a methacrylic acid polymer with divinylbenzene. Polacrilex resin is not included in a pharmacopoeia monograph, although the USP/NF contains a monograph for the potassium salt, Polacrilon potassium. Amberlite IRP64 is included in a number of UK approved oral products and is therefore not a novel excipient. The applicant’s specification for Amberlite includes controls of description, identity (IR), powder fineness (analytical sieving), residual methacrylic acid, loss on drying, sodium, iron, heavy metals, ion-exchange capacity and microbial quality. The applicant has justified omission of a control of residual solvents since no solvents are used in its production. This is acceptable. Proposed control limits of methacrylic acid have been justified in relation to EC tolerable daily intakes as applicable to packaging materials. In view of the use of Amberlite in other oral products, the proposed control limit may be accepted. This excipient and its proposed specification is supported by suitable certificates of analysis and this is considered satisfactory.

Control of Drug Product
A satisfactory finished product specification was finalised during assessment. At the request of MHRA the Market Authorisation holder provided further data on aspects of the analysis of the drug product including disintegration testing, description of microbial testing and dissolution testing.

Container Closure System
Tablets are packed into either PCTFE-PE-PVC/Aluminium or Aluminium/Aluminium blister strips containing 28 or 56 tablets which meet current EU and Ph. Eur. packaging requirements and are supported by Certificates of Analysis.

Stability
Satisfactory stability batch data was provided supporting a shelf-life of 24 months in the blister packs. The Market Authorisation holder also committed to carry out post-approval long-term stability studies as per CPMP guideline CPMP/QWP/122/02 (CPMP is Committee for Proprietary Medicinal Products (known as CHMP - Committee for Medicinal Product for Human Use)).
Summary of Product Characteristics, Patient Information Leaflet and Packaging
The pharmaceutical assessor requested minor amendments to the SPC, PIL and packaging and these amendments were carried out.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE
A Marketing Authorisation was granted.
MEDICAL ASSESSMENT

1. INTRODUCTION

Risperidone is well known, and in the case of a generic product containing a widely used, well known active substance, no further clinical trials are required and none are provided by the applicant.

To support the application, the applicant has submitted a single bioavailability study comparing Risperdal Quicklet 4mg orodispersible tablets with Risperdal 4mg oral tablets.

2. BACKGROUND

Risperidone is well characterised in the literature. It is a member of the benzisoxazole derivatives, a family of antipsychotics.

Risperidone is an antipsychotic agent used to treat schizophrenia. The antipsychotic effect is thought to be related to its ability to block dopamine D2 receptors and serotonin (5-HT2) receptors. Risperidone is also a potent alpha1-adrenergic and histamine H1 antagonist. The pharmacodynamic effects of the major metabolite, 9-hydroxyrisperidone, are very similar to those of risperidone itself.

Compared to other antipsychotic drugs it may cause lower incidence of extrapyramidal adverse effects. Like many other antipsychotics, risperidone appears to increase the risk of cerebrovascular adverse events in elderly patients treated for behavioural disturbances as highlighted lately by regulators.

3. INDICATIONS

The applicant has submitted the following:

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

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

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

Risperdal Quicklet is not licensed for the treatment of behavioural symptoms of dementia.

This is identical to the text for the reference product and is satisfactory.

4. **DOSE & DOSE SCHEDULE**

These are consistent with the dose schedules for the reference product (Risperdal Quicklet, PL 00242/0378-80) and are satisfactory.

6. **CLINICAL PHARMACOLOGY**

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT$_2$ and dopaminergic D$_2$ receptors. Risperidone binds also to alpha$_1$-adrenergic receptors and, with lower affinity, to H$_1$-histaminergic and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent D$_2$ antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

The pharmacokinetics of Risperidone are well described. Risperidone is extensively metabolized in the liver by cytochrome P450 2D6 to a major active metabolite, 9-hydroxyrisperidone, which appears approximately equipotent with risperidone, with respect to receptor binding activity. Consequently, the clinical effect of the drug likely results from the active moiety (the combined concentrations of risperidone plus 9-hydroxyrisperidone). The hydroxylation of risperidone, and hence the concentrations of parent drug and active metabolite, differ substantially in extensive and poor CYP2D6 metabolizers. However, the concentration of the active moiety does not differ substantially between extensive and poor metabolizers, and elimination half-lives are similar in all subjects (20 to 24 hours).

A single centre, single dose, randomised, open, two-period, cross-over bioequivalence study of Risperdal Quicklet 4mg orodispersible tablets (Janssen-Cilag, FR) versus Risperidone 4mg tablets (Janssen-Cilag, FR) in schizophrenic patients is presented.

**Study**

Forty (32 male and 8 female) schizophrenic patients, aged 20-61 years, were included in this study. Each subject received one of the 2 risperidone formulations. The patients continued taking their prescribed antipsychotic medication (those already taking rispiridone were excluded from the study) except on the dosing day. For each
subject there were 2 dosing periods, with a washout period of 10 days. A randomisation scheme was included in the report. The following formulations were administered:

Reference: Risperdal 4mg tablet (Janssen-Cilag, FR, Batch No: D03LC1028)

Test: Risperidone Disintegrating 4mg orodispersible tablets (Janssen-Cilag, FR, Batch No: D03LC1037)

The reference is registered in France.

The tablets were administered with 240 ml water, the orodispersible tablets after moistening tongue with saliva after >10hr fast. Standard meals were administered from 4 hours post-dose. Subjects were free to drink additional supplied water from 2 h post-dose. Blood samples were taken at pre-dose and at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours after administration of the products. Plasma samples were analysed for Risperidone and 9-OH Risperidone. The method was validated and the validation report was provided.

AUC\((0-t)\), AUC\((0-inf)\), C\(_{max}\), t\(_{max}\) and t\(_1/2\) were calculated according normal standard procedures.

Statistical evaluation was performed for AUC\((0-t)\), AUC\(_{inf}\) and C\(_{max}\) with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

The study was conducted in accordance with GCP and GLP. The report is of good quality.

The randomisation scheme was balanced for sequence and appears random.

Log-transformed data for AUC\(_t\), AUC\(_{inf}\) and C\(_{max}\) were analysed by ANOVA. T\(_{max}\) was analysed non-parametrically.

Results

There were no major protocol deviations or sequence or period effects.

Bioequivalence results for ln-transformed test/reference ratios with 90% Confidence Intervals:

**Active Moiety:**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_t)</td>
<td>102.92</td>
<td>(100.03-105.90)</td>
</tr>
<tr>
<td>AUC(_{inf})</td>
<td>102.89</td>
<td>(99.99-105.88)</td>
</tr>
<tr>
<td>C(_{max})</td>
<td>87.77</td>
<td>(83.13-92.67)</td>
</tr>
</tbody>
</table>

**Riperidone**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_t)</td>
<td>102.38</td>
<td>(96.28-108.87)</td>
</tr>
<tr>
<td>AUC(_{inf})</td>
<td>102.09</td>
<td>(95.66-108.94)</td>
</tr>
</tbody>
</table>
Bioequivalence has been satisfactorily demonstrated in accordance with CPMP criteria.

7. **EFFICACY**

No new data are submitted and none are required for this type of application.

8. **SAFETY**

No new data are submitted and none are required for this type of application.

9. **EXPERT REPORTS**

A satisfactory expert report was provided by a suitably qualified individual.

10. **PATIENT INFORMATION LEAFLET (PIL)**

The PIL should be modified in line with changes to the SPC.

11. **LABELLING**

The labelling complies with statutory requirements including full colour mock-ups and is satisfactory.

12. **APPLICATION FORM (MAA)**

The MAA is medically satisfactory.

13. **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The SPC underwent some minor amendments and is satisfactory.

14. **DISCUSSION AND CONCLUSION**

The SPC was amended and this was reflected in the PIL. Bioequivalence to the reference product was established. A Market Authorisation was granted.
Overall Conclusion and Risk/Benefit Analysis

Quality

The quality aspects of Risperdal Quicklet 3mg and 4mg Orodispersible Tablets 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.

Pre-Clinical

No new pre-clinical data were presented or were required for this type of application.

Clinical

No formal data on clinical efficacy or safety was presented for this application. A bioequivalence study was carried out. Changes were made to the Summary of Product Characteristics, PIL and packaging to satisfy current requirements.

Risk/Benefit Analysis

The quality of the products, Risperdal Quicklet 3mg and 4mg Orodispersible Tablets, is acceptable and the product is essentially similar to the reference product which has a positive risk/benefit assessment. A Marketing Authorisation was granted.
Steps Taken During Assessment

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the application on 19th November 2004.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 6th January 2005.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 31st August 2005 and 24th March 2006.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant provided further information in regard to the quality assessment on 31st January 2006 and 4th July 2006.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 7th December 2006.</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Risperdal Quicklet 3 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each orodispersible tablet contains 3 mg of risperidone.

Each orodispersible tablet contains 1.125 mg of aspartame

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Orodispensible tablets

Coral, round, biconvex tablets, etched “R 3”

4 CLINICAL PARTICULARS

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

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

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

Risperdal Quicklet is not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).
4.2 **Posology and method of administration**

**Method of administration**

**Oral use.**

The Risperdal Quicklet tablet should be placed on the tongue. It begins disintegrating in the mouth within seconds and can be swallowed subsequently with or without water. The mouth should be empty before placing the tablet on the tongue.

As the tablets are fragile, they should not be pushed through the foil as this will cause damage. Open blister by pulling up the edge of the foil and peeling it off, then tip the tablet out. After removal from its blister, the Risperdal Quicklet tablet should be consumed immediately as it cannot be stored once removed. No attempt should be made to split the tablet.

For doses lower than 3 mg other strengths or oral formulations of Risperdal should be used as Risperdal Quicklet must not be divided.

### 4.2.a Schizophrenia:

Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while Risperdal Quicklet therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperdal Quicklet therapy in place of the next scheduled injection. The need for continuing existing antiparkinson medication should be re-evaluated periodically.

**Adults**

Risperdal Quicklet may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day Risperdal Quicklet. The dosage may be increased to 4 mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.

**Elderly**

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

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

Renal and liver disease

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperdal Quicklet should be used with caution in this group of patients until further experience is gained.

4.2.b Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

As with all symptomatic treatments, the continued use of Risperdal must be evaluated and justified on an ongoing basis.

Elderly

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Renal and liver disease

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperdal 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 Risperdal with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of risperidone producing lower plasma levels of the antipsychotic fraction of Risperdal (see Section 4.5). It is therefore not recommended to co-administer Risperdal 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 Risperdal.

4.3 Contraindications

Risperdal Quicklet is contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.
Risperdal Quicklet 3 mg contains 1.125 mg aspartame and therefore should not be taken by patients with phenylketonuria.

4.4 Special warnings and precautions for use

**Elderly patients with dementia**

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including 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 (67-100).

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

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

**Cerebrovascular Adverse Events (CVAE)**

Risperdal Quicklet is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks). Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomised clinical trials conducted in elderly (>65 years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with risperidone, compared with placebo. Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33, 7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with Risperdal (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, atrial fibrillation, etc.

**Alpha-blocking activity**
Due to the alpha-blocking activity of Risperdal Quicklet, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperdal Quicklet 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, Risperdal 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 Risperdal Quicklet.

**Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)**

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

**Neuroleptic malignant syndrome (NMS)**

Neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all antipsychotic drugs including Risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency.

Caution should also be exercised when prescribing Risperdal Quicklet to patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

**Hyperglycemia**

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperdal. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

**Other**

Classical neuroleptics are known to lower the seizure threshold. Caution is recommended when treating patients with epilepsy.
As with other antipsychotics, patients should be advised of the potential for weight gain.

Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

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

As with Risperdal tablets and liquid, 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.

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions.
Cerebrovascular accidents have been observed during treatment with risperidone. (see Section 4.4 Special warnings and Precautions for Use).

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

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

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

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

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

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

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

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

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

4.9 Overdose
In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should be considered.
Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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

5 PHARMACOLOGICAL PROPERTIES

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

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-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, 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. As with Risperdal® Tablets and Liquid, 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.

Risperdal orodispersible tablets and oral solution are bio-equivalent to Risperdal oral tablets.

5.3 **Preclinical safety data**
There are no preclinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
Polacrilex resin (methacrylic acid polymer with divinylbenzene)
Gelatin type A
Mannitol
Glycine
Simethicone
Carbomer
Sodium hydroxide
Aspartame
Red ferric oxide (E172)
Peppermint oil
Xanthan gum

6.2 **Incompatibilities**
No incompatibilities known.

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
Do not store above 30°C.
Store in the original container

6.5 **Nature and contents of container**
Blister strips consisting of:

Polychlorotrifluoroethylene (PCTFE) film, polyvinylchloride (PVC) film, polyethylene (PE) film with a backing comprising of aluminium foil, polyester film and paper (film/foil).

Or
Polyvinylchloride (PVC) film, aluminium foil, polyamide (oPA) film with a backing comprising of aluminium foil, polyester film and paper (foil/foil).

The strips are packed in cardboard cartons to contain 28 or 56 tablets per pack.

6.6 Special precautions for disposal
Please refer to Section 4.2. Posology and Method of Administration.

7 MARKETING AUTHORISATION HOLDER
Janssen-Cilag Ltd
Saunderton
High Wycombe
Buckinghamshire
HP14 4HJ
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 00242/0407

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/12/2006

10 DATE OF REVISION OF THE TEXT
07/12/2006
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Risperdal Quicklet 4 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each orodispersible tablet contains 4 mg of risperidone.

Each orodispersible tablet contains 1.5 mg of aspartame

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Orodispersible tablets

Coral, round, biconvex tablets, etched “R 4”

4 CLINICAL PARTICULARS

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

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

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

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

4.2 Posology and method of administration
Method of administration

Oral use.

The Risperdal Quicklet tablet should be placed on the tongue. It begins disintegrating in the mouth within seconds and can be swallowed subsequently with or without water. The mouth should be empty before placing the tablet on the tongue.

As the tablets are fragile, they should not be pushed through the foil as this will cause damage. Open blister by pulling up the edge of the foil and peeling it off, then tip the tablet out. After removal from its blister, the Risperdal Quicklet tablet should be consumed immediately as it cannot be stored once removed. No attempt should be made to split the tablet.

For doses lower than 4 mg other strengths or oral formulations of Risperdal should be used as Risperdal Quicklet must not be divided.

4.2.a Schizophrenia:

Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while Risperdal Quicklet therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperdal Quicklet therapy in place of the next scheduled injection. The need for continuing existing antiparkinson medication should be re-evaluated periodically.

Adults

Risperdal Quicklet may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day Risperdal Quicklet. The dosage may be increased to 4 mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

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

Renal and liver disease

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperdal Quicklet should be used with caution in this group of patients until further experience is gained.

4.2.b Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

As with all symptomatic treatments, the continued use of Risperdal must be evaluated and justified on an ongoing basis.

Elderly

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Renal and liver disease

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperdal 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 Risperdal with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of risperidone producing lower plasma levels of the antipsychotic fraction of Risperdal (see Section 4.5). It is therefore not recommended to co-administer Risperdal 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 Risperdal.

4.3 Contraindications

Risperdal Quicklet is contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.
Risperdal Quicklet 4 mg contains 1.5 mg aspartame and therefore should not be taken by patients with phenylketonuria.

4.4 Special warnings and precautions for use

Elderly patients with dementia

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including 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 (67-100).

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

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

Cerebrovascular Adverse Events (CVAE)

Risperdal Quicklet is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks). Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomised clinical trials conducted in elderly (>65 years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with risperidone, compared with placebo. Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33, 7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with Risperdal (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, atrial fibrillation, etc.

Alpha-blocking activity
Due to the alpha-blocking activity of Risperdal Quicklet, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperdal Quicklet 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, Risperdal 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 Risperdal Quicklet.

**Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)**

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

**Neuroleptic malignant syndrome (NMS)**

Neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all antipsychotic drugs including Risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency.

Caution should also be exercised when prescribing Risperdal Quicklet to patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

**Hyperglycemia**

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperdal. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

**Other**

Classical neuroleptics are known to lower the seizure threshold. Caution is recommended when treating patients with epilepsy.
As with other antipsychotics, patients should be advised of the potential for weight gain.

Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

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

As with Risperdal tablets and liquid, 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.

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions.
Cerebrovascular accidents have been observed during treatment with risperidone. (see Section 4.4 Special warnings and Precautions for Use).

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

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

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

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

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

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

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

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

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

4.9 Overdose

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should be considered.
Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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

5 PHARMACOLOGICAL PROPERTIES

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

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-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, 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. As with Risperdal® Tablets and Liquid, 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.

Risperdal orodispersible tablets and oral solution are bio-equivalent to Risperdal oral tablets.

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Polacrilex resin (methacrylic acid polymer with divinylbenzene)
Gelatin type A
Mannitol
Glycine
Simethicone
Carbomer
Sodium hydroxide
Aspartame
Red ferric oxide (E172)
Peppermint oil
Xanthan gum

6.2 Incompatibilities
No incompatibilities known.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C.
Store in the original container

6.5 Nature and contents of container
Blister strips consisting of:

Polychlorotrifluoroethylene (PCTFE) film, polyvinylchloride (PVC) film, polyethylene (PE) film with a backing comprising of aluminium foil, polyester film and paper (film/foil).

Or
Polyvinylchloride (PVC) film, aluminium foil, polyamide (oPA) film with a backing comprising of aluminium foil, polyester film and paper (foil/foil).

The strips are packed in cardboard cartons to contain 28 or 56 tablets per pack.

6.6 **Special precautions for disposal**
Please refer to Section 4.2. Posology and Method of Administration.

7 **MARKETING AUTHORISATION HOLDER**
Janssen-Cilag Ltd
Saunderton
High Wycombe
Buckinghamshire
HP14 4HJ
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00242/0408

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
07/12/2006

10 **DATE OF REVISION OF THE TEXT**
07/12/2006
Labels and Leaflet
RISPERDAL® QUICKLET®
riperidone

Information for people taking Risperdal Quicklet Orodispersible Tablets
This leaflet contains important information. Before you start to take your medicine, please read it carefully all the way through. If there is anything that you do not understand or if you need more information or advice, you should ask your pharmacist, nurse or doctor who will be pleased to help you.
This leaflet applies only to Risperdal Quicklet. Please do not throw it away as you may need to refer to it again.

REMEMBER - This medicine has been prescribed for you only.

What is your medicine? The name of your medicine is Risperdal Quicklet and its active ingredient is risperidone. The tablets are orodispersible, which means that they break up in the mouth and can be taken with or without water. Each Risperdal Quicklet tablet contains 0.5 mg, 1 mg, 2 mg, 3 mg or 4 mg risperidone.

Each tablet also contains several inactive ingredients which allow it to be made. These are: polyvinyl resin, gelatin, mannitol (E421), glycine,-smethylene, carboxymethyl sodium hydroxide, aspartame, peppermint oil and red ferric oxide (E172). The 3 mg and 4 mg strengths also contain xanthan gum.

Note: Aspartame (E951) is a source of phenylalanine and may be harmful for people with phenylketonuria.

The following packs are registered, (not all packs are marketed): 0.5 mg tablets (round, light coral, biconvex, etched “R0.5”), 8, 28 or 56 tablets.
1 mg tablets (square, light coral, biconvex, etched “R1”), 8, 28 or 56 tablets.
2 mg tablets (round, light coral, biconvex, etched “R2”), 8, 28 or 56 tablets.
3 mg tablets (round, coral, biconvex, etched “R3”), 28 or 56 tablets.
4 mg tablets (round, coral, biconvex, etched “R4”), 28 or 56 tablets.

Who has made your medicine? The Product Licence holder is Janssen-Cilag Ltd, Saunders, High Wycombe, Buckinghamshire HP14 4HU, UK. The tablets are manufactured by Janssen-Cilag SpA, Latina, Italy or Janssen Pharmaceuticals N.V. Beerse, Belgium or McGeorge Cory Ltd, Banbury, UK.

What is your medicine for? Risperdal Quicklet is one of a group of medicines called antipsychotics. It is used to treat conditions which affect the way you think, feel and/or act. These conditions may cause symptoms such as confusion, hallucinations (e.g hearing, seeing or sensing things which are not there), delusions, unusual suspiciousness (paranoia), emotional and social withdrawal. People with these conditions may also feel depressed, guilty, anxious or tense. Risperdal Quicklet may be taken for both sudden (acute) and long-lasting (chronic) disorders.

In addition, Risperdal Quicklet may be used to control the symptoms of mania for people with bipolar disorder.

When should Risperdal Quicklet not be used? Do not use Risperdal Quicklet if you have ever had an allergic reaction to risperidone or any of the ingredients listed in the “What is your medicine?” section above. An allergic reaction may be recognised as a rash, itching, swollen face or lips, or shortness of breath. You should also not use this product if you were born with a condition called phenylketonuria.

Before taking your medicine, tell your doctor if you are pregnant, trying to become pregnant, or breast feeding. You should not breast feed if you are taking Risperdal Quicklet.

Risperdal Quicklet should not be used by children under the age of 15 years.

Ask your doctor for advice if:
- you are taking medicines for Parkinson’s disease
- you suffer from heart or blood vessel disease, liver or kidney disease, Parkinson’s disease, epilepsy or dementia
- you have had a stroke or transient ischaemic attack (temporary reduction in blood flow to the brain).

You should also tell your doctor if you have other risk factors for blood vessel disease, including high blood pressure, diabetes, current smoking or a heart disorder called atrial fibrillation.

Tell your doctor if you are taking buspirone. Buspirone is a drug which is sometimes used to treat high blood pressure, or to treat swelling of parts of the body caused by the build-up of too much fluid. Studies in elderly patients have shown that taking Risperdal in combination with buspirone may be harmful. Your doctor will decide if you can take Risperdal Quicklet and if this dose will need to be altered.

Always tell your doctor, nurse or pharmacist if you are taking any other medicines because taking some medicines together can be harmful.

If you are taking any of the following, taking Risperdal Quicklet as well may make you feel more drowsy:
- Medicines taken for anxiety or to help you to sleep (tranquilisers)
- Certain painkillers
- Some antihistamines (such as chlorpheniramine)
- Certain antidepressants.

Only take these medicines while you are on Risperdal Quicklet if your doctor says that you can.

A drug called carbamazepine, commonly used to treat epilepsy or facial neuralgia (severe pain attacks in the face), or others such as phenobarbital or paraldehyde (medicines for treating depression) may affect liver enzymes. This can change the effect of Risperdal Quicklet, so you should tell your doctor if you start or stop taking such medication, as you may need to take a different dose of Risperdal Quicklet.

While taking Risperdal Quicklet
- You should be careful how much alcohol you drink. The combined effect of Risperdal Quicklet and alcohol might make you feel drowsy.
- Risperdal Quicklet might affect your alertness so you should not drive or operate machinery until the doctor sees how the tablets affect you.
- If you have diabetes or you have a risk of getting diabetes, your doctor may check your blood sugar levels while you are taking Risperdal.

How to take Risperdal Quicklet
- The Risperdal Quicklet tablets are fragile. They must not be pushed through the packaging as this would damage them. To take a tablet out of the packaging:
  - pull up the edge of the foil and peel foil off completely
  - tip the tablet out
  - do not break or divide the tablets

UKPAR Janssen-Cilag Ltd, Risperdal Quicklet 3mg and 4mg Tablets 36
The tablet should be placed on the tongue as soon as it is removed from the packaging. It begins breaking up in the mouth within seconds and can then be swallowed with or without water. Your mouth should be empty before placing the tablet on the tongue. Your doctor will tell you how many Risperdal Quicklet tablets to take and for how long you should continue to take them. This will vary from person to person and your doctor will adjust the number and strength of the tablets to suit you.

For adults and adolescents over 15 years of age with conditions which affect the way they think, feel or act:

The dose will be started gradually over the first days of treatment as follows:
- Day 1: 2 mg
- Day 2: 4 mg

This can be taken as a single dose or as half the dose in the morning and half the dose in the evening. However, your doctor may recommend a more gradual increase.

Remember: You should not cut or divide these tablets in any way.

The dosage will then be set to suit your needs but it is usually between 4 mg and 8 mg a day. Some patients may require less than 4 mg for a good effect.

For adults and adolescents over 15 years of age with bipolar disorder:

If you need to take Risperdal to help control the symptoms of mania, a starting dose of 2 mg once a day is recommended, and your doctor will adjust the dose if necessary. Most people feel better with doses between 4 and 5 mg per day. Your doctor will tell you what dose suits your particular situation. Your treatment should be regularly reviewed and changed if appropriate.

Important - never take more than a total of 16 mg per day.
- Risperdal Quicklet is only for those aged 15 years and over.
- If you are elderly or have a liver or kidney disorder, you should take half the above doses. You will be told how many tablets you need to take.
- Do not stop your treatment just because you feel better. It is important that you carry on taking Risperdal Quicklet for as long as your doctor has told you to.
- If you miss a tablet, take your next tablet as usual and continue your course.
- If you stop taking Risperdal Quicklet, you should do so gradually, especially if you have been taking a high dose, unless your doctor has told you otherwise. Stopping treatment suddenly may cause effects such as feeling sick, vomitting, sweating, sleeplessness, muscle stiffness or jerky movements, or your original medical problem may come back. Always follow your doctor's instructions carefully.
- Always read the label. If you are in any doubt as to what tablets you should take you should contact your nurse or pharmacist.

If you think your medicine makes you feel ill

There are usually few side effects when Risperdal Quicklet is taken in the way your doctor, nurse or pharmacist has described. Do not be alarmed by this list of possible side effects. You may not have any of them.

Sometimes Risperdal Quicklet may cause side effects such as headache, sleeplessness, anxiety or agitation. Occasionally the following effects may occur: sleepiness, tiredness, dizziness, difficulty in concentrating, blurred vision, constipation, indigestion, feeling or being sick (nausea or vomiting), stomach ache, sexual potency problems, leakage of urine, rarer or blocked nose, liver problems, local skin rash or swelling, or other allergic reactions such as itching, swollen face or lips, or tightness of breath. Weight gain or swelling of the ankles may also occur.

Occasionally strokes or transient ischemic attacks may occur in people taking Risperdal. If you experience sudden weakness or numbness of the face, arms or legs, especially on one side, or instances of slurred speech, seek medical attention.

In very rare cases, high blood sugar has been reported. See your doctor if you experience symptoms, such as excessive thirst or urination.

Sometimes trembling, pronounced muscle stiffness or spasm, slowness of movement, excess salivation, restlessness or rolling of the eyes can occur but this will usually disappear if your dose of Risperdal Quicklet is reduced by your doctor or if your doctor prescribes you an additional medicine.

When used for a long time, women may suffer from milk secretion, an absence of menstrual periods or changes in the regularity of their periods. Men may experience breast swelling. If these persist, tell your doctor.

Occasionally, changes in blood cell count have been reported.

In some cases, your blood pressure may fall slightly in the early stages of the treatment, resulting in dizziness. This will usually pass off automatically. Somewhat later in the treatment, increased blood pressure may also occur, but this is very rare.

In rare cases, Risperdal Quicklet may cause a desire to drink large amounts of water. You might also experience marked changes in your body temperature or uncontrollable movements, mainly of the face or tongue. Rare cases of convulsions (fits) have also occurred. If any of these occur, contact your doctor as soon as possible.

Very rarely, Risperdal Quicklet might cause fever, faster breathing, sweating, muscle stiffness and reduced consciousness. If this occurs, stop taking the tablets and contact a doctor at once.

If continuous erection of the penis occurs, contact your doctor immediately.

If your medicine affects you in any other way, you should tell your doctor, nurse or pharmacist.

Please also refer to the 'Before you take Risperdal Quicklet' sections above.

How to store Risperdal Quicklet

As with all medicines, Risperdal Quicklet tablets should be kept in a safe place where children cannot reach or see them. Store the tablets in their original container. Do not store the tablets above 30°C. Do not use the tablets after the expiry date printed on the packaging. Always return any left-over medicine to your pharmacist. Only keep it if your doctor tells you to.

For information in large print, tape, CD or Braille, phone 0800 731 8450.

This leaflet was last approved in

© registered trademark

JANSSEN-CILAG Ltd