Public Assessment Report

Scientific discussion

Risperidon “Nycomed”
(Risperidone)

DK/H/1316/001-006/DC

This module reflects the scientific discussion for the approval of Risperidon “Nycomed”. The procedure was finalised at 12 August 2008. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

This assessment report concerns Risperidon “Nycomed”, film-coated tablets in the strengths 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 6 mg, approved through DCP on 12 August 2008 with Denmark acting as RMS.

The application is submitted in accordance with article 10 of Directive 2001/83/EC as amended. Essential similarity is claimed to Risperdal, film-coated tablets, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 6 mg registered in the UK since 8 December 1992. The active substance, risperidone, is the same as in the originator product. The efficacy and safety profile is therefore considered identical. A bioequivalence study of the Risperidone tablets has been performed with the reference product Risperdal 4 mg film-coated tablets, Janssen-Cilag AEBE, Greece.

Risperidon “Nycomed” is indicated for the treatment of:

- Schizophrenia; 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. Risperidon alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

- 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.

- Treatment of behavioural and other disruptive disturbances of oligophrenic children adolescents and adults in whom destructive symptoms (such as aggressiveness, activity disturbances, self-inflicted injury) are dominant and where non medical psycho-social therapy has not had adequate effect.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

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

According to the Guidelines on Pharmacovigilance for medicinal products for human use, NTA vol. 9A all MAHs must have an appropriate system of pharmacovigilance in place. The RMS considers the Pharmacovigilance system as described by the applicant is sufficient.

Risperidone is included in the EU HBD list. The next data lock point is May 2009 and the first PSUR must be submitted July 2009. A 3 year PSUR cycle will apply hereafter.
II. QUALITY ASPECTS

II.1 Introduction
Risperidon “Nycomed” is presented in the form of film-coated tablets containing 0.5, 1, 2, 3, 4 and 6 mg risperidone. The finished product is, to be marketed in opaque white PVC/PE/PVDC/Aluminium blister packs. The excipients are:

**Tablet core:**
Microcrystalline Cellulose, Starch Pregelatinised, Hypromellose, Magnesium stearate

**Film-coating:**
- **0.5 mg:** Hypromellose (E464). Titanium dioxide (E171). Talc. Propylene glycol. Quinoline yellow (E104).
- **1 mg:** Hypromellose (E464). Lactose monohydrate. Titanium dioxide (E171). Macrogol 4000.
- **2 mg:** Hypromellose (E464). Titanium dioxide (E171). Talc. Propylene glycol. Quinoline yellow (E104).
- **3 mg:** Hypromellose (E464). Titanium dioxide (E171). Talc. Propylene glycol. Sunset Yellow (E110).

II.2 2.2 Drug Substance
The active substance, risperidone, is described in the European Pharmacopoeia. It is a white or almost white powder. It is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol and it dissolves in dilute acid solutions. It is not optically active.

The chemical-pharmaceutical documentation from the drug substance manufacturer is presented as a CEP. The chemical-pharmaceutical documentation from the drug product manufacturer and Quality Overall Summary in relation to risperidone are of sufficient quality in view of the present European regulatory requirements.

The in-house control tests and specifications for the drug substance risperidone are adequately drawn up. The methods have been described and validated. Batch results are presented to cover all the specifications.

With regard to stability of the drug substance reference is made to the CEP. The retest period is 3 years if stored in double polyethylene bag kept in fibre drums.

II.3 Medicinal Product
The chemical-pharmaceutical documentation from the drug product manufacturer and Quality Overall Summary in relation to Risperidon Nycomed are of sufficient quality in view of the present European regulatory requirements.

The development of the product has been described, the choice of excipients is justified and their functions explained. The development of the dissolution method has been described.

The control tests and specifications for drug product are adequately drawn up. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 18 batches. The batch analysis results show that the finished products meet the proposed specifications.

The conditions used in the stability studies are according to the ICH stability guideline. A shelf-life of 36 months with storage conditions ‘store below 30°’ for the drug product is approved.
NON-CLINICAL ASPECTS

II.4 Discussion on the non-clinical aspects
Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

III. CLINICAL ASPECTS

III.1 Introduction
Risperidone is an antipsychotic drug belonging to the group of benzoxazole-derivatives. Risperidone is a selective monoaminergic antagonist with high affinity for both serotonergic 5-HT2 and dopaminergic D2 receptors. It is indicated for treatment of Schizophrenia, mania in bipolar disorder and behavioural and disruptive disturbances.

III.2 Pharmacokinetics

IV.2.1 General description
Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. Food does not affect the absorption of risperidone. Risperidone is partly metabolized to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. Together they make up the active (anti psychotic) fraction. Another metabolic pathway for risperidone is N-dealkylation. After oral administration to psychotic patients, risperidone is eliminated with a half life of approx. 3 hours and 9-hydroxy risperidone with an elimination half life of approx. 24 hours. Steady state for 9-hydroxy-risperidone is reached after 4-5 days dosing. Plasma concentrations are dose proportional within the therapeutic dose interval. Risperidone is quickly distributed in the body. The volume of distribution is 1-2 l/kg. In plasma risperidone is quickly bound to albumin and α-1-glucoprotein acid. Plasma-protein binding for risperidone is 88% and 77% for 9-hydroxy-risperidone. One week after administration 70% of the dose is excreted in the urine and 14% in feces. In urine 35-45% of the administered dose consists of risperidone and 9-hydroxy risperidone – the rest is inactive metabolites.

A single-dose study showed higher active plasma concentrations and a slower elimination of risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

The pharmacokinetics for risperidone, 9-hydroxy-risperidone and the active anti psychotic fraction in children, are comparative to that of the pharmacokinetics in adults, according to a study with six autistic children (3-7 years old). The mean terminal half-life, though, both for risperidone as well as for 9-hydroxy-risperidone was 30-35% lower than in adult subjects.

IV.2.2 Bioequivalence
To support the application, the applicant has submitted as report one single dose bioequivalence study. Risperidon Nycomed 4 mg film-coated tablets have been compared to Risperdal, Janssen Cilag, 4 mg film-coated tablets from the Greek market. The biowaiver for 0.5 mg, 1 mg, 2 mg, 3 mg and 6 mg strengths is accepted.

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting with a wash out period of 14 days between the two administrations. 4 mg was administered in each period.

26 healthy volunteers participated in the study. 22 subjects completed the study and their data were used in the statistical analysis (drop-outs: 2 did not show up for the first dosing and 2 did not show up for the second dosing).
Results/Discussion:

Table 1. Pharmacokinetic parameters (non-transformed values; geometric mean ± SD, $t_{\text{max}}$ median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-72}$ ng/ml/h</th>
<th>AUC$_{0-\text{last}}$ ng/ml/h</th>
<th>AUC$_{0-\infty}$ ng/ml/h</th>
<th>C$_{\text{max}}$ ng/ml</th>
<th>$t_{\text{max}}$ h</th>
<th>$T_{1/2}$ h</th>
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<tbody>
<tr>
<td>Test</td>
<td>164.619 CV(%) 97.75</td>
<td>148.374 CV(%) 99.30</td>
<td>187.177 CV(%) 91.47</td>
<td>27.606 CV(%) 54.75</td>
<td>1.300 (0.5-3.5)</td>
<td>5.669</td>
</tr>
<tr>
<td>Reference</td>
<td>171.652 CV(%) 101.47</td>
<td>157.186 CV(%) 109.34</td>
<td>191.962 CV(%) 102.73</td>
<td>27.172 CV(%) 44.23</td>
<td>1.500 (0.5-6)</td>
<td>5.575</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.9785 0.801.20</td>
<td>0.9619 0.81-1.15</td>
<td>1.0334 0.85-1.25</td>
<td>0.9460 0.81-1.11</td>
<td></td>
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</tbody>
</table>

*AUC$_{0-\infty}$: area under the plasma concentration-time curve from time zero to infinity
*AUC$_{0-\text{last}}$: area under the plasma concentration-time curve from time zero to last quantifiable concentration
*AUC$_{0-t}$: area under the plasma concentration-time curve from time zero to $t$ hours
*C$_{\text{max}}$: maximum plasma concentration
*$t_{\text{max}}$: time for maximum concentration
*T$_{1/2}$: half-life

*ln-transformed values

The ANOVA technique indicated that factors of period, treatment and sequence had no statistically significant effect on AUC$_{0-t}$, AUC$_{0-\infty}$, AUC$_{0-\text{last}}$ and C$_{\text{max}}$. Food effect was not part of this study.

No pre-dose levels are detected.

The confidence intervals for AUC$_{0-t}$, AUC$_{0-\infty}$, AUC$_{0-\text{last}}$, C$_{\text{max}}$ are all within the range 80-125%. This is acceptable.

The extrapolated AUC is more than 20% for 5 subjects receiving the test and for 3 subjects receiving the reference product. A discussion of the possible consequences for the conclusion of bioequivalence was requested by the RMS. The applicant’s response was considered acceptable.

Only raw data are presented for the active metabolite 9-OH-risperidone. This is in accordance with the BE guideline and therefore considered acceptable.

Conclusion:
The bioequivalence between the test product Risperidon “Nycomed” 4 mg film-coated tablets and the reference product Risperdal 4 mg film-coated tablets has been adequately demonstrated. Risperidon “Nycomed” is considered bioequivalent to Risperdal.

III.3 Discussion on the clinical aspects
Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.
IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a quality, non-clinical and clinical point of view the benefit/risk is considered positive and Risperidon “Nycomed” is recommended for approval.

The applicant has made the following commitments:

- The applicant commits to harmonise the SPC with the referral SPC (within 3 months) after completion of the SPC harmonisation Article 30 referral procedure for the risperidone innovator product.
- The applicant commits to harmonise the PIL in accordance with the referral SPC (within 3 months) after completion of the SPC harmonisation Article 30 referral procedure for the risperidone innovator product.
- Process validation will be performed on the first 3 production scale batches of each strength manufactured at proposed manufacturing site.
- Certificates of analysis performed on the first 3 consecutive production scale batches of each strength will be forwarded when available.
- The first 3 production batches of each strength will be put on stability and tested according to the stability protocol as presented in section P.8.1.
- A commitment is made by the Applicant to provide analytical results in accordance with rev 2 of the CEP to the authorities as soon as available.