LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Risperidon Mylan film-coated tablets (Risperidone)

SE/H/712/01-07/MR

This module reflects the scientific discussion for the approval of Risperidon Mylan. Please note that the marketing authorisation was first approved with the name "Risperidon Merck" and therefore this name is used throughout the document. The procedure was finalised at 24 May 2007. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Merck NM AB, Sweden has applied for a marketing authorisation for Risperidon Merck filmcoated tablets claiming essential similarity to Risperdal tablets marketed in Sweden by Janssen-Cilag AB. The product contains risperidone as active substance and is indicated for the treatment of

− The treatment of schizophrenia.
− Maintenance treatment in order to prevent relapse in chronic schizophrenia in patients having shown a response to initial treatment.
− The treatment of aggression and pronounced psychotic symptoms in patients with dementia in whom such disorders can cause suffering, potential danger or risk of self-harm in the patient.
− Treatment of manic episodes in association with bipolar disorder. Risperidone has not been shown to be effective in the prevention of relapses of manic or depressive episodes.
− Behavioural disorders according to DSM-IV in children (> 5 years of age), adolescents and adults in the form of impulse control disorders with aggression to self and/or others or inappropriate behaviour requiring treatment, associated with low intelligence (mental retardation). Treatment recommendation: Only for treatment initiated by a specialist in paediatric and adolescent psychiatry.
− Serious conduct/behavioural disorder in children with autism in the age group 5-12 years. Continued treatment of adolescents with autism where treatment was started in childhood. Treatment recommendation: Only for treatment initiated by specialist in paediatric neurology, paediatric psychiatry, adolescent psychiatry, or physicians who are well familiar with the treatment of autistic disorder.

The reference product used in the bio-equivalence study is the Risperdal 2 mg tablet from the UK market.

II. QUALITY ASPECTS

II.1 Introduction

Risperidone Merck is presented in the form of film-coated tablets containing 0.25, 0.5, 1, 2, 3, 4 or 6 mg of risperidone. The tablets are packaged in plastic/aluminium blisters.

II.2 Drug Substance

Risperidone is a white or almost white powder which is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol. It dissolves in dilute acid solutions. The structure of risperidone has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents. The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated. Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period adopted.

II.3 Medicinal Product

Risperidon Merck film-coated tablets are formulated using excipients described in the current Ph Eur, except for the film-coating agents, which are controlled according to acceptable in house specifications. All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01). The product development has taken into consideration the physico-chemical characteristics of the active substance. The manufacturing process has been sufficiently well described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification. The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose. Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refers 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.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The absorption of risperidone from the GI tract is rapid. The bioavailability is 60-90 % (higher in poor metabolisers with respect to CYP2D6 compared with extensive metabolisers) and independent of food intake. The plasma protein binding is approximately 90 %. Risperidone is metabolized by CYP2D6 to 9-hydroxy-risperidone. This metabolite has similar activity as the parent compound and the two are together referred to as “the active moiety” or the “antipsychotic fraction”. The pharmacokinetics of risperidone is independent of dose within the therapeutic range.

The pharmacokinetic documentation consists of one comparative, randomized, two-period, two-way, crossover, bioequivalence study of Risperidone 2 mg tablets versus Risperdal 2 mg tablets conducted in healthy participants subjects under fasting conditions. The absence of studies with the other tablet strengths is considered acceptable from a pharmacokinetic point of view, as the pharmacokinetics of risperidone is independent of dose within the therapeutic range. Risperidone and 9-hydroxy-risperidone were analysed in plasma by HPLC with electrochemical detection. The performance of the method was satisfactory. Bioequivalence was shown regarding C_{max} and AUC_{0-t}. In addition, data for 9-hydroxyrisperidone were supportive as bioequivalence was shown between test and reference formulations with respect to this active metabolite.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refers 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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Risperidon Merck film-coated tablets are recommended for approval.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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