LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Risperidon Dival film-coated tablets
Risperidone

SE/H/703/01-06/MR

This module reflects the scientific discussion for the approval of Risperidon Dival film-coated tablets. The procedure was finalised on 3 April 2007. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Dival Classics, Greece has applied for marketing authorisation for Risperidon Dival film-coated tablets claiming essential similarity to Risperdal® film-coated tablets, marketed by Janssen-Cilag GmbH. The product contains risperidone as active substance and is indicated for the treatment of

- Schizophrenia.
- Maintenance treatment in order to prevent relapse in chronic schizophrenia in patients having shown a response to initial treatment.
- 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.
- Manic episodes in association with bipolar disorder.
- Serious acting out conduct disorders such as behavioural disorder and oppositional defiant disorder according to DSM IV in children, adolescents and adults with psychological development disorders (mental retardation).
- Aggressive behaviour and irritability in children and adolescents with autism

The reference product used in the bio-equivalence study to support the applications is the Risperdal® tablets from Germany.

II. QUALITY ASPECTS

II.1 Introduction

Risperidon Dival is presented in the form of film-coated tablets containing 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg or 6 mg of risperidone. The excipients of the tablet core are lactose monohydrate, maize starch, microcrystalline cellulose, hypromellose, magnesium stearate, colloidal anhydrous silica, sodium lauril sulphate and the tablets are film-coated. The tablets are packaged in transparent PVC/PE/PVDC/Al blisters.

II.2 Drug Substance

The drug substance, risperidone, has a monograph in the Ph. Eur. Risperidone is a white to almost white powder. It is practically insoluble in water, freely soluble in methylene chloride and sparingly soluble in ethanol. It dissolves in dilute acid solutions. Risperidone exhibits polymorphism. Risperidone has no chiral centers and is thus an achiral substance. 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.

II.3 Medicinal Product

The tablet cores of Risperidon Dival film-coated tablet are formulated using excipients described in the current Ph Eur. The common ingredients of the coatings, hypromellose, titanium dioxide propylene glycol and talc also comply with their Ph. Eur. monographs. The colorants iron oxide red, black, and yellow (E172) comply with the JPE and NF. The colorants sunset yellow (E110), indigo carmine (E132) and quinoline yellow (E104) are all tested

according by the manufacturer of the colorants according to acceptable in-house specifications.. The raw materials used in the product has 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 described and critical steps have been 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 Summary of Product Characteristics.

III. NON-CLINICAL ASPECTS

III.1 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.

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 pharmacokinetic study performed with one strength of tablet. 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. The study was a single-dose, 2-way, crossover study in which the pharmacokinetics of risperidone and 9-hydroxy-risperidone were compared when administering risperidone orally in the fasting state. The two treatment phases were separated by 14 days. Analysis of the plasma samples was performed using a validated HPLC-MS/MS method. The performance of the method was satisfactory.

Bioequivalence was shown regarding C_{max} and AUC. In addition, data for 9-hydroxy-risperidone 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 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

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 Dival 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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