LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Risperidon STADA film-coated tablets
Risperidone

SE/H/683/01-06/MR

This module reflects the scientific discussion for the approval of Risperidon STADA film-coated tablets. Please note that the marketing authorisation was first approved with the name "Alstrips" and therefore this name is used throughout the document. The procedure was finalised on 20 March 2007. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

APS Alster Pharma Service GmbH has applied for marketing authorisations for the medicinal products Alstrisp film-coated tablets. Essential similarity to the originator Risperdal, marketed in Sweden by Janssen-Cilag AB is claimed. The product contains risperidone as active substance and is indicated for the treatment of

- Risperidone 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.
- The 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.

The reference product used in the bio-equivalence study is the 1 mg strength of Risperdal from the German market.

II. QUALITY ASPECTS

II.1 Introduction

Alstrisp is presented in the form of 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 6 mg film-coated tablets. The excipients of the tablet cores are lactose monohydrate, sodium lauril sulfate, microcrystalline cellulose, maize starch, magnesium stearate, and colloidal anhydrous silica. Depending on the strength, different colouring agents are used. The drug product is packaged in plastic-Al blisters or HDPE containers.

II.2 Drug Substance

Risperidone has a monograph in the European Pharmacopoeia. 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. 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

Alstrisp is formulated using excipients which all comply with the Ph. Eur., except for the various colour mixtures used in the film-coatings of the different strengths. The coating agents all comply with relevant EU Directives. Divisibility of tablet halves has been shown for the 0.5, 1, 2, 3 and 4 mg tablets, which are scored. The only material of animal origin used in the product is lactose monohydrate and the milk used for the manufacture of the lactose is collected as milk for human consumption. Thus, 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) has been demonstrated.
The manufacturing process has been sufficiently 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 stated 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

Risperidone is completely absorbed after oral administration, producing maximum plasma concentrations in 1-2 hours. Food has no significant effect on absorption. Risperidone is metabolised by the CYP2D6 isoenzyme to 9-hydroxyrisperidone, which has similar pharmacological effects as risperidone. Risperidone together with 9-hydroxyrisperidone produce the active antipsychotic effect. The plasma protein binding is 88 % for risperidone and 77% for 9-hydroxyrisperidone. After oral dosing, 70% of the dose is excreted in the urine (35-45 % of the dose as risperidone and 9-hydroxyrisperidone) and 14 % in the faeces. Risperidone shows linear pharmacokinetics.

The submitted pharmacokinetic documentation consists of one bioequivalence study comparing the 1 mg tablets applied for with Risperdal 1 mg tablets (Janssen-Cilag GmbH (Organon). This is satisfactory from a pharmacokinetic point of view as risperidone shows linear pharmacokinetics. The study had a randomized, single-dose, crossover design. Twenty-six volunteers entered and completed the study. Risperidone was administered under fasting conditions and blood sampling took place until 192 hours post-dose. The doses were separated by 2 weeks. Bioequivalence was demonstrated both for risperidone and 9-hydroxyrisperidone.

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 Alstrisp film-coated tablets are recommended for approval.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se