COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Risperidon Sandoz 0.5 mg, film-coated tablets (risperidone)

NL/H/5806/001

Date: 5 July 2023

This module reflects the scientific discussion for the approval of Risperidon Sandoz 0.5 mg, film-coated tablets. The procedure was finalised on 17 April 2007 in Germany (DE/H/0794/001/DC). After a transfer on 27 March 2023, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Risperidon Sandoz 0.5 mg, film-coated tablets, from Sandoz B.V.

A comprehensive description of the current indications and posology is given in the SmPC.

This decentral procedure concerns an application in accordance with article 10(1) of Directive 2001/83/EC (generic application) referring to the reference medicinal product Risperdal 1.0 mg film-coated tablets, authorised to Janssen-Cilag Ltd. (UK) in December 1992.

The reference member state (RMS) of the initial procedure was Germany and the Concerned Member States (CMS) were Austria, Czechia, Denmark, Finland, Norway, Poland, Sweden, Slovenia and United Kingdom. The RMS roll was transferred to the Netherlands on 27 March 2023.

General comments on the submitted dossier
The dossier is of generally satisfactory quality.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles
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. The bioequivalence study is stated to be compliant with the relevant guidelines for GCP.

II. QUALITY ASPECTS

II.1 Drug Substance

Risperidone is a benzisoxasol derivate with well-known antipsychotic properties. Risperidone is a potent antagonist at dopamine D_2 and serotonin 5-HT_2 receptors and exerts also antagonistic effects at α_1-receptors and to a lower extent at α_2- and H_1-receptors.

Four suppliers for the drug substance are registered. Reference is made to the Drug Master File (DMF) resp. CEP of each supplier. The EDMF–procedure is used resp. A valid Certificate of suitability has been submitted. The active substance risperidone supplied by the four API supplier complies to the Ph.Eur. monograph. The chemical-pharmaceutical documentation and Quality Overall Summary in relation to the drug products are of sufficient quality in view of the present European regulatory requirements. The control tests and specifications for drug substance product are adequately drawn up. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

II.2 Medicinal Product

The drug product has been developed to be essential similar to the innovator, Janssen-Cilag. The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on various batches. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf life of 2 years in Aclar blister strips and in HDPE-bottles without a special storage condition is justified by updated stability data.

III. NON-CLINICAL ASPECTS

Effective medical treatment of psychoses began in the early 1950's, when, starting with chlorpromazine, neuroleptic drugs became available. Conventional neuroleptics like the phenothiazines or butyrophenones with prominent antidopaminergic properties exert, however, also distinct sedative, extrapyramidal and hypotensive side effects which limit their clinical usefulness. Beginning with clozapine, a series of 'atypical' neuroleptics appeared with a differing scope of activity and a lesser degree of side effects allowing a more individualized therapy. Risperidone combines potent serotonin 5-HT_{2A}-receptor antagonism with dopamine D_2-receptor antagonism, a combination of effects supposed to reduce the occurrence of extrapyramidal side effects. Besides its effects in many animal models of dopaminergic activity risperidone has shown its efficacy in the clinical setting. Also, the safety profile may be derived from the side effect profile in man. Risperidone was well absorbed after p.o. and s.c. administration in rats and p.o. administration in dogs. Major metabolic pathways of risperidone in rats and dogs were the same as those in humans; the main metabolite was 9-hydroxy-risperidone, which is pharmacodynamically active comparable to risperidone. While risperidone is eliminated with a half-life of 3-4 h, 9-hydroxy-risperidone has a half-life of 20-24 h.

Chronic toxicity showed increase of prolactin concentrations and sequelae thereof. In rats reversible granular infiltrations of the prostate were seen in the highest dose group. In dogs, a reduction in testicular androgen production was a possible reason for disturbed spermatogenesis in males. Animals of all treatment groups showed an inhibition of ejaculation, which was at least partly caused by the alpha-adrenolytic activity of risperidone. Haemoglobin, haematocrit and erythrocyte count was decreased in middle and high dose groups. In animal experiments higher than therapeutic concentrations may induce QT-interval prolongation due to HERG channel blockade. There was no evidence for a mutagenic potential. Risperidone showed no teratogenic effects in rat and rabbits. In carcinogenicity studies observed tumours have been related to increased prolactin levels.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

This application concerns the 0.5 mg strength (film-coated tablets) of the active substance risperidone. A single bioequivalence study was performed with this strength in a dosage of 1.5 mg (3 x 0.5 mg) under fasting conditions. Based on the submitted bioequivalence study Risperidon 0.5 mg film-coated tablet (Hexal AG, Germany) is considered bioequivalent with Risperdal® 0.5 mg film-coated tablet (Janssen-Cilag GmbH, Germany).

IV.2 Risk Management Plan

The benefit/risk assessment for this product is considered to be positive for the proposed Indication (for the original procedure DE/H/0794/001/DC), see indications in chapter IV.2.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

In the proposed indication (for the original procedure DE/H/0794/001/DC)

“Severe behavioural disturbances associated with aggressiveness, impulsiveness and self-inflicted injury diagnosed according to DSM-IV criteria in children (at least 5 years of age), adolescents and adults with mental retardation. It is recommended, that Risperidon be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of behavioural disturbances of children and adolescents and disturbances in the mentally retarded”

The available data are satisfactory and conclusive to support the indication. The proposed indication is in line with the reference product and German originator and also with the procedures Risperidon FI/H/571-272+574-576/01/MR (finalized 5th July 2006).

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
1012431	RMS transfer from DE/H/0794/001 to NL/H/5806/001	Yes	05-04-2023	Yes	N.A.