

IPAR



**Public Assessment Report for a
Medicinal Product for Human Use**

Scientific Discussion

Perdamel 4 mg film-coated tablets
Risperidone
PA0126/169/006

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This product was initially authorised under procedure number SE/H/0685/002-006/MR with the SE as RMS. The responsibility of RMS was transferred to Ireland on 16/10/2019 under procedure number IE/H/1090/002-006/MR.

Please note the following detail for the product in IE:

Marketing Authorisation Number: PA0126/169/002-006

Marketing Authorisation Holder: Clonmel Healthcare Ltd

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRa website at www.hpra.ie.

The SE public assessment report published at the time of the initial marketing authorisation is provided herein.

APS Alster Pharma Service GmbH has applied for marketing authorisations for the medicinal products Rispalan 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.
- Risperidone is indicated for 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.
- The treatment of 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 (> 5 years of age), adolescents and adults with psychological development disorders (mental retardation).
- Serious conduct disorders in children (> 5 years of age) and adolescents with autism

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

II. QUALITY ASPECTS

I.1 Introduction

Rispalanis 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.

I.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.

I.3 Medicinal Product

Risipalan 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 Risiperdal 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 CONCLUSIONS

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 Rispalanfilm-coated tablets are recommended for approval.

VI. REVISION DATE

14/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From SE/H/0685/002-006 to IE/H/1090/002-006/MR			