IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Risperidone 1mg/ml Oral Solution
Risperidone
PA0281/248/001

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/1174/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 07th March 2018 under procedure number IE/H/0996/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/248/001
Marketing Authorisation Holder: Pinewood Laboratories Ltd.

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

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

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Risperidone 1mg/ml oral solution, in the treatment of acute and chronic schizophrenic psychoses and for the treatment of mania in bipolar disorder, is approvable.

The application for Risperidone 1mg/ml oral solution is abridged application made according to Article 10(1) of Directive 2001/83/EC submitted within the Decentralised Procedure with the UK acting as the Reference Member State (RMS). The only Concerned Member State (CMS) is Ireland (IE). The reference medicinal product refer to Janssen-Cilag Ltd Risperdal Liquid (PL 00242/0199) for the 1mg/ml oral solution.

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to alpha$_1$-adrenergic receptors and, with lower affinity, to H_1-histaminergic and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

The RMS has been assured that acceptable standards of GMP are in place for this product types at all sites responsible for the manufacture and assembly of this product.

ABOUT THE PRODUCT

Name of the product in the Reference Member State	Risperidone 1mg/ml oral solution
Name(s) of the active substance(s) (INN)	Risperidone
Pharmacotherapeutic classification (ATC code)	N05AX
Pharmaceutical form and strength(s)	1mg/ml oral solution
Reference numbers for the Mutual Recognition Procedure	UK/H/1174/01/DC
Reference Member State	United Kingdom
Member States Concerned	IE
Marketing Authorisation Number(s)	PL 29831/0349
Name and address of the authorisation holder	Wockhardt UK Limited, Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF, UK

II. QUALITY ASPECTS

SCIENTIFIC OVERVIEW AND DISCUSSION

DRUG SUBSTANCE

The active substance is the subject of DMF.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Active risperidone is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of three years is accepted and is supported by stability data.

DRUG PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients, namely Disodium Edetate, purified water, Malic acid, Sodium Saccharin, Potassium Hydroxide, Sodium Methylparaben and Hydroxypropyl Betadex.

All excipients used comply with their respective European Pharmacopoeial monograph.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

Impurity profiles
Satisfactory information was provided on levels of impurities in the proposed product.

Manufacture
A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is packaged in amber glass bottle. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging comply with EU legislation regarding contact with solutions for parenteral and ophthalmic use Directive 2002/72/EC (as amended).

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with no storage conditions is set, which is satisfactory.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
It is recommended that Marketing Authorisation is granted for this application.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

III. NON-CLINICAL ASPECTS

No new preclinical data have been supplied with this application and none are required for an application of this type.

IV. CLINICAL ASPECTS

1. INTRODUCTION
This is an outgoing Decentralised application for Risperidone 1mg/ml Oral Solution. This abridged standard application is submitted under Article 10(1) of Directive 2001/83/EC. The applicants Risperidone Oral solution claim equivalence to Risperdal Liquid, 1mg/ml (PL 00242/0199) first authorisation was granted to Janssen-Cilag Limited in the U.K. on 21st November 1995.

2. INDICATIONS
Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses and other psychotic conditions in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

Risperidone is not licensed for the treatment of behavioural symptoms of dementia.

3. DOSE & DOSE SCHEDULE
1 ml of Risperidone Oral Solution contains 1 mg risperidone. If necessary Risperidone Oral Solution may be diluted with mineral water, orange juice or black coffee. When diluted in this way, the product should be used immediately. The liquid should not be mixed with tea.
(See Section 6. Pharmaceutical Particulars).

a Schizophrenia:
Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while risperidone therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating risperidone therapy in place of the next scheduled injection. The need for continuing existing antiparkinson medication should be re-evaluated periodically.

Adults
Risperidone Oral Solution may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day risperidone. The dosage may be increased to 4 mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Children
Use of risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

Renal and liver disease
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperidone should be used with caution in this group of patients until further experience is gained.

b Bipolar Mania:

Adults
Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.
As with all symptomatic treatments, the continued use of risperidone must be evaluated and justified on an ongoing basis.

Elderly
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Renal and liver disease
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.
Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers
There is limited information on the combined use of risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of risperidone producing lower plasma levels of the antipsychotic fraction of risperidone (see Section 4.5). It is therefore not recommended to co-administer risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of risperidone.

Method of administration
Oral use.

4. TOXICOLOGY
No new data.

5. CLINICAL PHARMACOLOGY

A randomised single, single dose, open-label, two-treatment, two-period, two-sequence, crossover comparative bioavailability study on Risperidone 1mg/ml oral solution (Wockhardt Limited India) compared with Risperidal Liquid (containing human subject under fasting condition).

Table No. 1 Investigational Product

Test product (A)	Risperidone 1mg/ml oral solution (Manufactured by; Wockhardt Limited, India)
Reference product (B)	Risperdal Liquid

	(Containing Risperidone 1mg/ml oral solution (Product Licence Holder: Janssen –Cilag Ltd UK

This was a two way crossover study of standard design in 12 subjects. All 12 subjects were included in the analyses and no issues were identified with the design or conduct of the study. Results were as follows:

Table No. 2a: Summary of PK & Statistical Results calculated for Risperidone in 12 subjects (01 to 12)

Parameters (unit)	Geometric Least Squares Mean N = 12			90 % Confidence Interval	Intra CV (%)	Power (%)
	Test (A)	Reference (B)	% Ratio (A/B)			
C_{max} (ng/mL)	9.2715	9.6929	95.65 %	84.79 % -107.91 %	16.40 %	85.70 %
AUC_{0-t} (ng.hr/mL)	60.7239	63.2291	96.04 %	85.68 % -107.64 %	15.51 %	89.13 %
$AUC_{0-\infty}$ (ng.hr/mL)	62.6491	65.0298	96.34 %	86.27 % -107.58 %	15.00 %	90.94 %

Figure No. 1a: Mean Plasma Concentration Time Curve for Risperidone

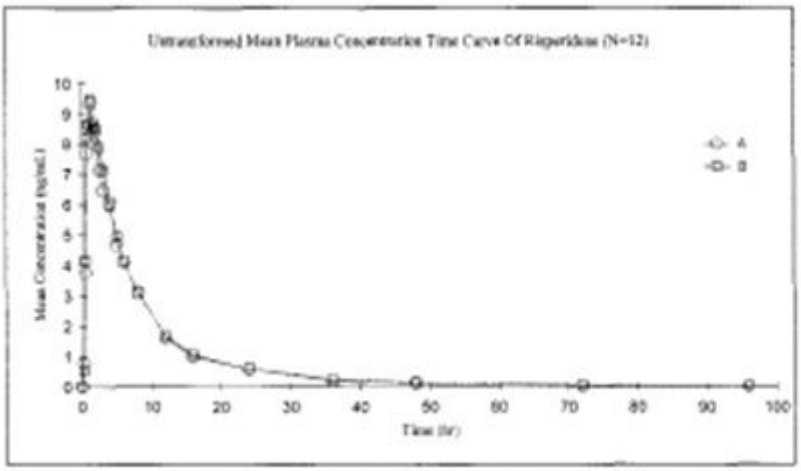
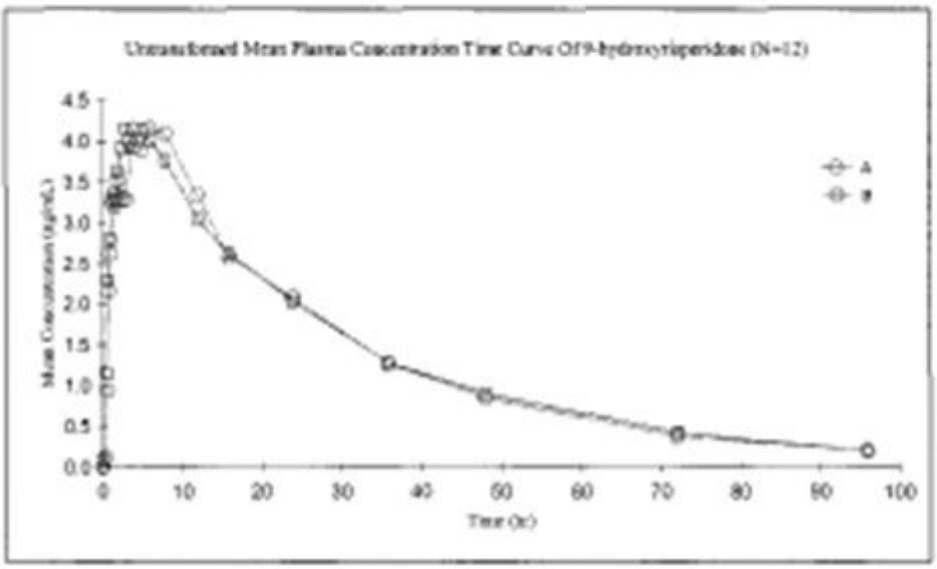


Table No. 2 b: Summary of PK & Statistical Results calculated for 9-hydroxyrisperidone in 12 subjects (01 to 12)

Parameters (unit)	Geometric Least Squares Mean N = 12			90 % Confidence Interval	Intra CV (%)	Power (%)
	Test (A)	Reference (B)	% Ratio (A/B)			
C_{max} (ng/mL)	3.6858	4.0201	91.69 %	76.13 % -110.41 %	25.52 %	47.97 %
AUC_{0-t} (ng.hr/mL)	112.3341	114.2734	98.30 %	89.27 % -108.25 %	13.08 %	96.13 %
$AUC_{0-\infty}$ (ng.hr/mL)	120.4917	122.3717	98.46 %	90.04 % -107.67 %	12.13 %	97.77 %

Figure No. 2a: Mean Plasma Concentration Time Curve for 9-hydroxyrisperidone

Figure No. 2a: Mean Plasma Concentration Time Curve for 9-hydroxyrisperidone



Bioequivalence was confirmed for the parent. Intra-individual variability was markedly higher for the metabolite and as a consequence 90% CIs for C_{max} were wide and fell outside 80-125%. However this is not of concern for the following reasons.

1. In the light of discussions at the EWP PK group the UK's current view is that it is not required that bioequivalence be shown for 9-OH risperidone, as kinetics are linear.
2. The study was powered to show bioequivalence for the parent not for the metabolite and the failure to meet the 80-125% criteria for C_{max} for 9-OH risperidone reflects this fact. The 90% CIs are wide and include unity. These results do not suggest a true difference between formulations.

In conclusion bioequivalence to the reference product has been established.

6. EFFICACY

No new data.

7. SAFETY

No new data.

8. EXPERT REPORTS

A satisfactory expert report is provided by an appropriately qualified physician.

9. PATIENT INFORMATION LEAFLET (PIL)

This is satisfactory.

10. LABELLING

Full colour mock-ups are provided. The labelling is medically satisfactory.

11. APPLICATION FORM (MAA)

The MAA is medically satisfactory.

12. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is satisfactory.

13. MEDICAL CONCLUSION

Marketing Authorisations may be granted for this application.

V. OVERALL CONCLUSIONS

Marketing Authorisations may be granted for this application.

VI. REVISION DATE

August 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/1174/001/DC to IE/H/0996/001/DC	N/A	N/A	N/A	Approved 07/03/2018
MA Transfer	CRN00C40X	SmPC, Leaflet Old MA holder: Wockhardt UK Limited New MA Holder: Pinewood Laboratories Ltd OLD PA number: PA1339/014/007 New PA number: PA0281/248/001	29/01/2021	29/01/2021	Approved