CBG MEB

# PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

# Risperidon Sandoz 1 mg, film-coated tablets
# Risperidon Sandoz 2 mg, film-coated tablets
# Risperidon Sandoz 3 mg, film-coated tablet\s
# Risperidon Sandoz 4 mg, film-coated tablets

## Sandoz B.V., the Netherlands

## risperidone

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/1031/01-04/MR**
**Registration number in the Netherlands: RVG 34202-34205**

**December 1st, 2008**

| | |
|---|---|
| Pharmacotherapeutic group: | Antipsychotica; other |
| ATC code: | N05AX08 |
| Route of administration: | oral |
| Therapeutic indication: | schizophrenia; maintenance treatment of clinically improvement in patients who responded to initial treatment with risperidone; severe aggression in patients with advanced forms of dementia; moderate to severe manic episodes. |
| Prescription status: | prescription only |
| Date of authorisation in NL: | October 18th 2006 |
| Concerned Member States: | Mutual recognition procedure with AT, DE, DK, ES, FI, IE, IT and LU |
| Application type/legal basis: | Directive 2001/83/EC, Article 10(1) |

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

# I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Risperidon Sandoz 1, 2, 3 and 4 mg, film-coated tablets, from Sandoz B.V., the Netherlands. The date of authorisation was on October 18th 2006 in the Netherlands.

The product is indicated for the treatment of schizophrenia. Besides this, risperidone is also effective as maintenance treatment of clinically improvement in patients who responded to initial treatment with risperidone. Risperidone is indicated for the treatment of severe aggression in patients with advanced forms of dementia, and for the treatment of moderate to severe manic episodes.

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

Risperidone, a benzisoxazol derivative, is part of a special class of antipsychotic active substances. Risperidone is a mono-aminergic antagonist. It shows a high affinity for the serotonine-5-$HT_2$ - and dopamine-$D_2$ receptors. Risperidone binds to the $\alpha_1$-adrenergic receptor and, with a lower affinity to the histamine-$H_1$ and $\alpha_2$-adrenergic receptor. Risperidone does not have any affinity for the cholinergic receptor.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Risperdal 1, 2, 3 and 4 mg film-coated tablets (NL License RVG 16096, 16097, 16098 and 16099), containing 1, 2, 3 and 4 mg risperidone respectively, which has been registered in the Netherlands by Janssen-Cilag B.V. since 1994. In addition, reference is made to Risperdal authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Risperdal 2 mg film-coated tablets, registered in Austria. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference product.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

# II SCIENTIFIC OVERVIEW AND DISCUSSION

## II.1 Quality aspects

**Compliance with Good Manufacturing Practice**
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

**Active substance**
The active substance is risperidone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU. Risperidone is a white or almost white powder. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur, with additional specifications for residual solvents, residual palladium, heavy metals, crystal form and particle size. Batch analytical data demonstrating compliance with this specification have been provided for 4 batches from one manufacturer and 1 batch from the othermanufacturers.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Stability data on the active substance have been provided for one manufacturer for 3 batches and for the second manufacturer for 4 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 24 months. Based on the data in the ASMFs, a retest period could be granted of 2 years without further storage conditions.

**Medicinal Product**

Composition
Risperidon 1 mg, film-coated tablets contain as active substance 1 mg risperidone and are white, oblong tablets with scoreline on one side.
Risperidon 2 mg, film-coated tablets contain as active substance 2 mg risperidone and are pink, oblong tablets with scoreline on both sides.
Risperidon 3 mg, film-coated tablets contain as active substance 3 mg risperidone and are yellow, oblong tablets with scoreline on one side
Risperidon 4 mg, film-coated tablets contain as active substance 4 mg risperidone and are dark pink, oblong tablets with scoreline on both sides.

The tablets are packed in PVC/PE/PVDC/Al blisters and PP tablet-containers.

Excipients
The excipients are:
Core: lactose monohydrate, microcrystalline cellulose (E460), pregelatinised (maize) starch, croscarmellose sodium, sodium laurilsulphate, silica (colloidal anhydrous) and magnesium stearate (E470b).

Coating:
Risperidon 1 mg: hypromellose (E464), titanium dioxide (E171), macrogol (400).
Risperidon 2 mg: hypromellose (E464), titanium dioxide (E171), macrogol (400), ferric oxide (red) (E172).
Risperidon 3 mg: hypromellose (E464), titanium dioxide (E171), macrogol (400), quinoline yellow, aluminum lake (E104).
Risperidon 4 mg: hydroxypropyl cellulose (E463), hypromellose (E464), titanium dioxide (E171), ferricoxide (red) (E172), ferric oxide (black) (E172).

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs, except for the Opadry coatings, for which in-house specifications were provided.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be bioequivalent with the innovator product Risperdal 1, 2, 3 and 4 mg film-coated tablets.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process is a common and standard process. Process validation data on the product have been presented for 9 pilot scale batches and 5 production scale batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished product is based on the monograph for tablets in the Ph.Eur. and includes tests for appearance, dimensions, identification of risperidone and colorants, loss on drying, related substances, dissolution rate, content uniformity, assay and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The MAH committed to perform breakability studies on all strengths.
Satisfactory validation data for the analytical methods have been provided.

Batch analytical data of 9 pilot-scale batches and 9 full-scale batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Comparative composition
A discussion is given on the qualitative composition and reference to the Note for Guidance is made to justify the use of the Austrian reference product. The quantitative composition of the Austrian Risperdal 2 mg has been sent in by the Austrian Authorities to the Reference Member State and the use is acceptable in the bioequivalence study.

Comparative dissolution profiles
Comparative dissolution studies were performed in 3 different media (pH 1, 4 and 6.8) with the test batch Risperidone Sandoz 2 mg and with the originator product Risperdal 2 mg (Janssen-Cilag Pharma, Austria). Initially buffer pH 6.8 was selected for the medium, but a wide scatter was observed in the results for the proposed product (including stability results) and the EU innovator products from Austria and Finland. According to the Guideline on the investigation of bioavailability and bioequivalence risperidone is a highly soluble active substance. Considering the observed scatter in the dissolution results of both the innovator products and the product under consideration it can be concluded that the quality of the product under consideration is sufficient, but the proposed testing conditions and specifications are insufficient to properly describe the quality of the product.
Several options to improve the testing conditions were discussed by the applicant. In line with literature reference from the innovator dissolution method and specification, the applicant considered it justified to change the dissolution medium and apply the 45 minutes time point for the developed product as well. Since the dissolution medium of 0.1 N HCl proved to be unsuitable due to bad chromatograms, a dissolution medium of 0.01 N HCl was tried. This dissolution medium, in combination with the 45 minutes time-point proved to be suitable since the scatter in dissolution results is similar and within an acceptable range for both for the innovator products and the developed product. The stability study of the risperidone 1, 2, 3 and 4 mg tablets will be continued using both dissolution methods. Since the innovator has a 45 minute time point and uses 0.1N HCl, there is no objection against the use of this time point, and neither is there an objection against the use of 0.01N HCl (instead of 0.1N HCl), as both water and 0.01N HCl are standard dissolution media.
The MAH committed to provide comparative dissolution profiles of Risperidon Sandoz 1, 3 and 4 mg at acetate buffer and 0.01 N HCl. Besides, three other commitments remain regarding impurity profiles and comparative dissolution data (see list post-approval commitments on page 8).

Stability tests on the finished product
Stability data on the product have been provided for 18 batches of accordance with applicable European guidelines demonstrating the stability of the product over 36 months. On basis of the data submitted, a shelf life was granted of 24 months, without further storage conditions. Four post-approval commitments were made by the MAH regarding stability; (1) The MAH committed to re-assess the impurity specifications when 24 months of stability data are available for batches manufactured with drug substance from one active substance manufacturer. (2) The MAH committed to put the first 2 production batches of the product on stability (for each type of packaging) and test these according to the stability protocol. (3) The MAH committed to provide stability data of batches taken with drug substance from one active substance manufacturer. (4) The MAH committed to perform the in-use stability study for a future commercial batch as one time activity.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

## II.2 Non clinical aspects

This product is a generic formulation of Risperdal, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of risperidone released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 II.3 Clinical aspects

Risperidone is a well-known active substance with established efficacy and tolerability.

The SPC is in line with the SPC as approved for procedure NL/H/916-918 (Risperidon AET 0.25, 0.5, 1, 2, 3, 4, 6 and 8 mg tablets) except for product names, marketing authorisation holder, marketing authorisation number and all chemical-pharmaceutical sections.

Since the starting dose and dose increase of 0.25 mg twice daily for the treatment of severe aggression in patients with advanced forms of dementia cannot be performed with the products under consideration, the MAH has included the following statement in section 4.2 during the mutual recognition procedure: *"For doses not realisable/practicable with these strengths, other strengths are available."*

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Risperidon Sandoz 2 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Risperdal 2 mg film-coated tablets.

A open, single-dose, randomised, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 26 healthy subjects (13 males and 13 females), aged 19-37 years. Each subject received a single dose (2 mg) of one of the 2 risperidone formulations. For each subject there were 2 dosing periods, separated by a washout period of 14 days. The tablet was orally administered with 240 ml water after a 10 h fasting period. Blood samples were collected at pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours after administration of the products. Two subjects were excluded because of personal reasons and protocol violation. Subsequently, 24 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of risperidone under fasted conditions.

| **Treatment N=24** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-\infty}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 52 ± 36 | 54 ± 37 | 14.3 ± 6.6 | 1.0 (0.5 – 3.0) | 2.5 ± 1.2 |
| **Reference** | 52 ± 39 | 53 ± 40 | 13.7 ± 6.7 | 1.0 (0.5 – 3.0) | 2.4 ± 1.2 |
| ***Ratio(90% CI)** | 1.06 (0.95 - 1.18) | 1.07 (0.96 - 1.19) | 1.07 (0.92 - 1.23) | -- | -- |
| **CV (%)** | 22.2% | 21.4% | 29.5% | -- | -- |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life

**ln-transformed values*

Risperidone should be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of risperidone. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence. The 90% confidence intervals calculated for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of risperidone under fasted conditions, it can be concluded that Risperidon Sandoz 2 mg film-coated tablets and the Risperdal 2 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 1, 3 and 4 mg film-coated tablets are dose proportional with the 2 mg film-coated tablet, with the minor exception of the colour coating. The pharmacokinetics of the active substance are linear in the range 1-4 mg. The results of the bioequivalence study performed with the 2 mg film-coated tablets therefore apply to the other strengths.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan

Risperidone was first approved in 1992, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of risperidone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. Questions were asked about all parts of the leaflet. The results show that the package leaflet meets the criteria for readability as set in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Risperidon 1, 2, 3 and 4 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Risperdal 1, 2, 3 and 4 mg film-coated tablets. Risperdal is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The SPC is in line with the SPC as approved for procedure NL/H/916-918 except for product names, marketing authorisation holder, marketing authorisation number and all chemical-pharmaceutical sections.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other risperidone containing products.

The Board followed the advice of the assessors. Risperidon Sandoz 1, 2, 3 and 4 mg, film-coated tablets were authorised in the Netherlands on October 18th 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for 1, 2, 3 and 4 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on July 31st 2007.

The PSUR submission cyclus is 3 years. The first PSUR will cover the period from July 2007 till July 2010.

The date for the first renewal will be: July 31st 2012.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product – comparative impurity and dissolution profiles

- The MAH committed to provide comparative dissolution profiles of Risperidon Sandoz 1, 3, and 4 mg at acetate buffer and 0.01 N HCl.
- The MAH committed to provide comparative dissolution data for the Italian reference products 1 mg and 4 mg versus Risperidon Sandoz 1 and 4 mg at acetate buffer and 0.1 N HCl.
- The MAH committed to provide the comparative impurity profiles between the test product and the Italian reference product as soon as innovator samples are available and analysis is completed.
- The MAH committed to provide the comparative dissolution profiles of the test products Risperidon Sandoz 1, 2, 3 and 4 mg versus the Polish reference products Rispolept 1, 2, 3, 4 mg, Janssen Pharmaceutica N.V. within 30 calendar days.

Quality – medicinal product - stability

- The MAH committed to perform breakability studies on all strengths.
- The MAH committed to re-assess the impurity specifications when 24 months of stability data are available for batches manufactured with drug substance from one active substance manufacturer.
- The MAH committed to put the first 2 production batches of the product on stability (for each type of packaging) and test these according to the stability protocol.
- The MAH committed to provide stability data of batches taken with drug substance from one active substance manufacturer.
- The MAH committed to perform the in-use stability study for a future commercial batch as one time activity.

## List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| ATC | Anatomical Therapeutic Chemical classification |
| AUC | Area Under the Curve |
| BP | British Pharmacopoeia |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| $C_{max}$ | Maximum plasma concentration |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CV | Coefficient of Variation |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EU | European Union |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| MEB | Medicines Evaluation Board in the Netherlands |
| OTC | Over The Counter (to be supplied without prescription) |
| PAR | Public Assessment Report |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| PSUR | Periodic Safety Update Report |
| SD | Standard Deviation |
| SPC | Summary of Product Characteristics |
| $t_{½}$ | Half-life |
| $t_{max}$ | Time for maximum concentration |
| TSE | Transmissible Spongiform Encephalopathy |
| USP | Pharmacopoeia in the United States |

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Type of modification | Date of start of the procedure | Date of end of procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| Change in name of the medicinal product in the Netherlands. | NL/H/1031/ 001-004/IB/ 001 | IB | 18-12-2007 | 17-1-2008 | Approval | N |
| Change in test procedure of the finished product. Minor change to an approved test procedure. | NL/H/1031/ 003/IA/002 | IA | 28-2-2008 | 13-3-2008 | Approval | N |