CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Risperidon disper CF 0.5 mg, 1 mg, and 2 mg orodispersible tablets
Centrafarm Services B.V., the Netherlands

risperidone

EU-procedure number: NL/H/1746/001- 003/MR
Registration number in the Netherlands: RVG 31887-9

7 May 2010

Pharmacotherapeutic group:	other antipsychotics
ATC code:	N05AX08
Route of administration:	oral
Therapeutic indication:	schizophrenia; moderate to severe manic episodes associated with bipolar disorders; persistent aggression in patients with moderate to severe Alzheimer's dementia; persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria.
Prescription status:	prescription only
Date of first authorisation in NL:	3 November 2006
Concerned Member States:	Mutual recognition procedure with ES, FR, PT (all strenghts); AT, BE, LU, and PL (only 1 mg and 2 mg)
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 member states have granted a marketing authorisation for Risperidon disper CF 0.5 mg, 1 mg, and 2 mg orodispersible tablets, from Centrafarm Services B.V. The date of authorisation was on 3 November 2006 in the Netherlands. The product is indicated for:

- treatment of schizophrenia
- Risperidon disper CF is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.
- short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others
- short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment

Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

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

Risperidon disper CF contains the active ingredient risperidone, which is an atypical antipsychotic that combines the known antipsychotic effects of dopamine antagonism, seen in classical antipsychotic, with serotonin antagonism.
Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone also binds to alpha1-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, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Risperdal 0.5 mg, 1 mg, and 2 mg tablets (NL license RVG 22714, 16096, and 16097) which have been registered in the Netherlands by Janssen-Cilag B.V. since 1999 (0.5 mg) and 1994 (1 mg and 2 mg) (original product). The data-protection period is determined by the reference product Risperdal, authorised since 1992 in the UK. 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 Quicklet orodispersible 1 mg tablets, registered

in Germany. 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. This generic product can be used instead of its reference product.

No new pre-clinical 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, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

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 this product type 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.*). The active substance is a white or almost white crystalline powder which is practically insoluble in water, freely in methylene chloride, and sparingly in ethanol 96%. It dissolves in dilute acid solutions. The CEP procedure is used for the active substance.

Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture
The manufacturing process is covered by the CEPs and therefore assessed by the EDQM.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEPs. The specification is acceptable in view of the various European guidelines. Batch analytical data have been provided for 3 batches per manufacturer demonstrating compliance with the specification.

Stability of drug substance
The stability has been covered by the CEPs claiming a retest period of 4 years for the drug substance derived from one manufacturer and 3 years for the drug substance from another manufacturer. The substance was adequately stored. The packaging materials have also been included on the CEPs. This has been assessed by the EDQM and is considered to be acceptable.

Medicinal Product

Composition
Risperidon disper CF 0.5 mg, 1 mg, and 2 mg are formulated as round, slightly biconvex, pink marbled, orodispersible tablets. The tablets are packaged in OPA/Al/PVC/AL blisters.

The excipients are: mannitol (E 421), butylated methacrylate copolymer, povidone, microcrystalline (E460) cellulose, hydroxy propyl cellulose, aspartame (E 951), crospovidone, iron oxide red (E172), flavour peppermint, flavour spearmint, calcium silicate, magnesium stearate (E572).

The excipients and packaging are usual for this type of dosage form. The 3 tablet formulations are dose proportional. The tablets differ in size, not in shape. There are no imprints or embossments and no break scores.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Development studies are briefly described. The process of making the final choice of the proposed composition has been clearly clarified.
The tablets disintegrate in 10-20 seconds in purified water at 37ºC. Tablet disintegration is sufficiently rapid for an orodispersible dosage form.
Comparative dissolution data on the Dutch (NL) Risperdal Quicklets were submitted. All samples had dissolved completely by the first sampling time (t=10 minutes). The composition of the DE 1 mg reference tablets used in the biostudy is sufficiently similar to the composition of the NL 1 mg innovator tablets. The *in-vitro* drug dissolution is sufficiently similar to support the generic application. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
Two granulates are made by wet granulation. The granules are mixed and then compressed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches. The product is manufactured using conventional manufacturing techniques. The MAH has committed to perform process validation on the first three production batches.

Excipients
The excipients with the exception of the spearmint and peppermint flavours, comply with the Ph.Eur. or the USP*. These specifications are acceptable. The spearmint and peppermint flavours comply with the food additives and flavourings directive 88/388/EC.

Microbiological Attributes
The Ph. Eur. limits are adopted.

Quality control of drug product
The product specification includes tests for appearance, identification, uniformity of dosage units by uniformity of content, disintegration time, dissolution time, related substances assay, and microbiological purity. This is considered to be acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches and the bio-batch, demonstrating compliance with the release specification.

Stability tests on the finished product
Stability data on the product has been provided for 9 pilot-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are in accordance with the ICH stability guideline. The batches were stored in blisters of OPA/Al/PVC sealed with aluminium foil. At accelerated conditions no out of specification results were observed in any of the batches. A slight decrease in water content was observed. This is considered to be acceptable.

In contrary to the water content at accelerated conditions no decrease in water content was observed at long term conditions. In all batches a decrease in assay was observed.
All parameters stayed within their limits. The claimed shelf-life of three years when stored in the original packaging in order to protect from moisture, can be granted.
The MAH committed has to submit full-scale stability studies over the full shelf-life when available.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

* *Ph.Eur and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and the United States, respectively.*

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 Clinical aspects

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Risperidon disper CF 1 mg orodispersible tablets (Centrafarm Services B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Risperdal Quicklet orodispersible 1 mg tablets (Janssen-Cilag, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

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

Study design
An open-label, randomised, single-dose, two-way cross-over bioequivalence study was carried out under fasted conditions in 36 healthy male subjects. Each subject received a single dose (1 mg) of one of the 2 risperidone formulations. The tablets were administered after a 10 hour fasting period. The subjects were instructed to let the orodispersible tablet completely dissolve on the tongue before swallowing the saliva. Once the drug was completely dissolved and swallowed, 100 ml tepid water was administered to each subject. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected predose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Risperidone may 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*.

Results
All 36 subjects completed the study. According to the protocol, data from the first 34 subjects was used for pharmacokinetic and statistical analysis.

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

Treatment N=34	**AUC_t** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	44170 ± 54461	45051 ± 55330	6312 ± 3329	1.67 (0.67-4.0)	5.02 ± 4.10
Reference	44950 ± 54030	45892 ± 55085	6350 ± 2850	1.33 (1-2.5)	5.14 ± 5.06
***Ratio (90% CI)**	0.95 (0.87 – 1.03)	0.95 (0.87 – 1.03)	0.97 (0.89 – 1.06)	---	---
CV (%)	---†	---†	---	---	---

$AUC_{0-\infty}$ 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*
† The CV values ar left out as the PK is not highly variable

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 9-hydroxy risperidone under fasted conditions.

Treatment N=34	**AUC_t** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	154907 ± 60322	165627 ± 62863	5753 ± 3152	4.0 (1.67 – 24.0)	24.54 ± 5.45
Reference	159854 ± 60367	171129 ± 64010	5802 ± 2947	4.0 (1.33 – 1.36)	24.73 ± 4.92
***Ratio (90% CI)**	0.97 (0.92 – 1.02)	0.97 (0.92 – 1.02)	0.98 (0.93 – 1.03)	---	---
CV (%)	---†	---†	---	---	---

$AUC_{0-\infty}$	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*
† The CV values ar left out as the PK is not highly variable

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 and supported by the data of 9-hydroxy risperidone under fasted conditions, it can be concluded that Risperidon disper CF 1 mg orodispersible tablets and Risperdal Quicklet orodispersible 1 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The 0.5 mg, 1 mg, and 2 mg tablets have a dose linear composition, and are produced at the same site. Dissolution was rapid (>80 within 30 minutes) at pH 1.2 and 6.8. In purified water, at pH 4.5, dissolution of risperidone was considerably slower. However, dissolution was similar between Test and Reference product at all three PH levels. Therefore, the results of the study carried out with the 1 mg formulation can be extrapolated to the other strengths (0.5 and 2 mg), according to conditions in *Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98*, section 5.4.

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.

Product information

SPC
The SPC was brought in line with the SPC of the innovator product Risperdal, which was harmonised during referral procedure EMEA/H/A-30/911.

Readability test
The PIL has been harmonised with the innovator Risperdal following an article 30 referral. Therefore, user testing was not considered necessary. However, the MAH did submit a readability test (performed in March 2007), which had been used in a previous procedure concerning Risperidone (eg. NL/H/918 and NL/H/921). The PIL tested was not identical to the PIL submitted with the application. The MAH has submitted a bridging statement in addition to the readability test, which is acceptable.

The test concerned a combined patient information leaflet for risperidone film coated tablets 0.25/0.5/1/2/3/4/6 mg. The test was performed with 20 test participants in two test rounds.

The MAH justified bridging the test considering that the package leaflet applies to the same active substance and the same strengths. Furthermore, the difference in dosage form is minimal and is not relevant for the text. All major sections, ie indications, contraindications, warnings and precautions for use,

posology, interactions, pregnancy and lactation, driving and using machines and undesirable effects have been addressed in the questionnaire. The questionnaire used in the test is equally applicable to Risperidon disper CF 0.5/1/2 mg.
Overall, the report is of good quality and the results show that the PIL fulfils the criteria as set in the readability guideline.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Risperidon disper CF 0.5 mg, 1 mg, and 2 mg orodispersible tablets have a proven chemical-pharmaceutical quality and are generic form of Risperdal 0.5 mg, 1 mg, and 2 mg 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Risperidon disper CF 0.5 mg, 1 mg, and 2 mg orodispersible tablets were authorised in the Netherlands on 3 November 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 essential similarity has been demonstrated for Risperidon disper CF 0.5 mg, 1 mg, and 2 mg orodispersible tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 25 February 2010.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from 25 February 2010 to 12 May 2012.

The date for the first renewal will be: 11 January 2013

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

Quality - medicinal product

- The MAH has committed to perform process validation on the first three production batches.
- The MAH has committed to submit full-scale stability studies over the full shelf-life when available.

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
PIL	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 the procedure	Approval/ non approval	Assessment report attached