CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Risperidon CF 0.25, 0.5, 1, 2, 3, 4, 6 and 8 mg film-coated tablets Centrafarm Services 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/918/01-08/MR
Registration number in the Netherlands: RVG 30896-30903
December 2nd 2008

Pharmacotherapeutic group:	Antipsychotica; other
ATC code:	N05AX08
Route of administration:	oral
Therapeutic indication:	schizophrenia; severe aggression in patients with advanced forms of dementia; and moderate to severe manic episodes in patients with bipolar affective disorder.
Prescription status:	prescription only
Date of authorisation in NL:	June 15th 2006 for the 1, 2, 3, 4, 6 and 8 mg strengths August 23rd 2006 for the 0.25 and 0.5 mg strengths
Concerned Member States:	Mutual recognition procedure with HU and PL for the 0.25, 0.5 and 8 mg strenght. Mutual recognition procedure with AT, CZ, EE, HU, LT, LV, PL and SK for the 1, 2, 3, 4 mg strenght. Mutual recognition procedure with AT, CZ, HU and PL for the 6 mg strenght.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1): - For the 0.5 and 8 mg strengths in NL. - For the 1, 2, 3 and 4 mg strengths in AT, CZ, EE, HU, LT, LV, PL and SK. - For the 6 mg strength in AT and PL. Directive 2001/83/EC, Article 10(3): - For the 0.25 strength in HU and PL - For the 0.5 and 8 strengths in HU and PL. - For the 6 mg strenght in CZ and HU.

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 CF 0.25, 0.5, 1, 2, 3, 4, 6 and 8 mg film-coated tablets, from Centrafarm Services B.V., the Netherlands. The date of authorisation in the Netherlands was on June 15th 2006 for the 1, 2, 3, 4, 6 and 8 mg strengths and August 23rd 2006 for the 0.25 and 0.5 mg strengths. Risperidone is indicated for the treatment of schizophrenia. Furthermore, risperidone is also effective: as a therapy to maintain clinical improvement in patients having shown a response to initial treatment, in the treatment of severe aggression in patients with advanced forms of dementia and in the treatment of moderate to severe manic episodes.

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. Risperidone is indicated for the treatment of moderate to severe manic episodes.

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

Risperidone is a benzisoxazole derivative; as such, it does not belong to the traditional class of antipsychotic agents. Risperidone is a monoaminergic antagonist. It has a high affinity for both the serotonin 5-HT_2 receptor and the dopamine D_2 receptor. Risperidone also binds to the alpha$_1$-adrenergic receptor and, with lower affinity, to the histamine H_1 and alpha$_2$ adrenergic receptors. Risperidone has no affinity for the cholinergic receptor.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Risperdal 0.5, 1, 2, 3, 4, 6, 8 mg film-coated tablets (NL License RVG 22714, 16096, 16097, 19098, 16099, 19585 and 19586 respectively), which have been registered in the Netherlands by Janssen-Cilag B.V., the Netherlands since 1994 (Risperdal 1, 2, 3 and 4 mg), 1998 (Risperdal 6 and 8 mg) and 1999 (Risperdal 0.5 mg). Risperdal 8 mg has been withdrawn from the Netherlands on December 31st 2007. 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 for the 0.5, 1, 2, 3, 4, 6 and 8 mg strengths. The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC for the 0.25 mg strength, as the 0.25 mg strength of the innovator product Risperdal is not registered in the Netherlands. Therefore, the applicant makes use of a hybrid application for the 0.25 mg strength with Risperdal 0.5 mg as the reference product.

In the concerned member states the applications will be submitted with the following legal bases:

AT: 1-6 mg: Article 10 (1) generic application
CZ: 1-4 mg: Article 10 (1) generic application
6 mg: Article 10 (3) hybrid application
EE: 1-4 mg: Article 10 (1) generic application
HU: 0.25, 0.5 mg: Article 10 (3) hybrid application
1-4 mg: Article 10 (1) generic application
6, 8 mg: Article 10 (3) hybrid application
LT: 1-4 mg: Article 10 (1) generic application
LV: 1-4 mg: Article 10 (1) generic application
PL: 0.25, 0.5 mg: Article 10 (3) hybrid application
1-6 mg: Article 10 (1) generic application
8 mg: Article 10 (3) hybrid application
SK: 1-4 mg: Article 10 (1) generic application

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 German reference product Risperdal 1 mg tablet. 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 its 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 and excipients
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. The active substance 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. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

The Active Substance Master File (ASMF) procedure is used for 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. The MAH committed to submit a type II variation to update the DMF. A new Ph.Eur. Certificate of Suitability for an active substance has been submitted through a IA variation, therefore the post-approval commitment has been resolved (see also page 11 Steps taken after the finalisation of the initial procedure).

Stability data on the active substance have been provided for 4 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 24 months. Based on the data submitted, a retest period could be granted of 2 years when stored at room temperature.

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 polydextrose, the colorants quinoline yellow aluminium lake (E104), FD&C yellow #6 sunset yellow FCF aluminium lake (E110), FD&C blue #2 indigo carmine aluminium lake (E132) and yellow iron oxide. For polydextrose in-house specifications where used. For quinoline yellow aluminium lake (E104), FD&C yellow #6 sunset yellow FCF aluminium lake (E110) and FD&C blue #2 indigo carmine aluminium lake (E132) the specifications of AMFarbVO were used. AMFarbVO is the German regulation for colourants for pharmaceutical use. And for yellow iron

oxide (E172) USP specifications were used. USP is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the USA. Furthermore, Opadry is a well-known used colouring for coating and a declaration of the supplier of the Opadry suspensions is presented stating that each colorant used complies with Directive 94/45/EC.

Medicinal Product

Composition
The tablet cores of the 0.25 and 0.5 mg tablets are qualitatively identical and dose proporitonal. The tablet cores of the other six strengths are qualitatively identical to the 0.25 and 0.5 mg tablets, but not dose proportional.

Risperidon CF 0.25 mg film-coated tablets contain as active substance 0.25 mg risperidone and are orange, oblong film-coated tablets, debossed “R” on one side and “0.25” on the other side of the tablet.
Risperidon CF 0.5 mg film-coated tablets contain as active substance 0.5 mg risperidone and are brownish-red, oblong film-coated tablets, scored on one side, debossed “R” on the scored side and “0.5” on the other side of the tablet
Risperidon CF 1 mg film-coated tablets contain as active substance 1 mg risperidone and are white, oblong film-coated tablets, scored on one side, debossed “R” on one side and “1” on the other side of the score. The opposite side of the film-coated tablet is plain.
Risperidon CF 2 mg film-coated tablets contain as active substance 2 mg risperidone and are salmon, oblong film-coated tablets, scored on one side, debossed “R” on one side and “2” on the other side of the score. The opposite side of the film-coated tablet is plain.
Risperidon CF 3 mg film-coated tablets contain as active substance 3 mg risperidone and are yellow, oblong film-coated tablets, scored on one side, debossed “R” on one side and “3” on the other side of the score. The opposite side of the film-coated tablet is plain.
Risperidon CF 4 mg film-coated tablets contain as active substance 4 mg risperidone and are light green, oblong film-coated tablets, scored on one side, debossed “R” on one side and “4” on the other side of the score. The opposite side of the film-coated tablet is plain.
Risperidon CF 6 mg film-coated tablets contain as active substance 6 mg risperidone and are yellow, round film-coated tablets, debossed “R” on one side and “6” on the other side of the tablet.
Risperidon CF 8 mg film-coated tablets contain as active substance 8 mg risperidone and are blue, round film-coated tablets, debossed “R” on one side and “8” on the other side of the tablet.

The film-coated tablets are packed in transparent PVC/PE/PCTFE-Al blisters and white HDPE tablet containers with white polypropylene screw cap.

The excipients are:
Tablet core: lactose monohydrate, sodium laurilsulfate, microcrystalline cellulose, maize starch, magnesium stearate (E 470b), silica colloidal anhydrous (E 551).

Film coating
0.25 mg: polyvinyl alcohol (partially hydrolysed), macrogol 3350, titanium dioxide (E171), talc, iron oxide yellow (E172).
0.5 mg: polyvinyl alcohol (partially hydrolysed), ,macrogol 3350, titanium dioxide (E171), talc, iron oxide red (E172).
1 mg: titanium dioxide (E171), polydextrose, hypromellose 3 cP (E464), hypromellose 6 cP, triethyl citrate, hypromellose 50 cP, macrogol 8000.
2 mg: polyvinyl alcohol (partially hydrolysed), macrogol 3350, titanium dioxide (E171), talc, FD&C yellow #6/sunset yellow FCF aluminium lake (E110).
3 mg: polyvinyl alcohol, partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc, quinoline yellow aluminium lake (E104), FD&C yellow #6 sunset yellow FCF aluminium lake (E110).
4 mg: polyvinyl alcohol, partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc, quinoline yellow aluminium lake (E104), FD&C blue #2 indigo carmine aluminium lake (E132)

6 mg: polyvinyl alcohol, partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc, quinoline yellow aluminium lake (E104), iron oxide yellow (E172), FD&C yellow #6 sunset yellow FCF aluminium lake (E110).
8 mg: polydextrose, titanium dioxide (E171), hypromellose 3 cP (E464), hypromellose 6 cP, glycerol triacetate, FD&C blue #2 indigo carmine aluminium lake (E132), macrogol 8000.

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.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the products have been presented for 3 batches of 0.25 and 0.5 mg, 2 batches of 1 mg and 1 batch of 2, 3, 4, 6 and 8 mg 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, identity risperidone, identity colorant, hardness, disintegration, dissolution, uniformity of content, related substances, assay and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Sufficient batch analytical data of pilot and production scaled batches have been provided for all strengths, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches per strength in accordance with applicable European guidelines demonstrating the stability of the product over 36 months when stored in blisters and when stored in tablet containers. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage conditions are*: "Do not store above 30°C.", "Keep the blister in the outer carton in order to protect from light."* and *"Store in the original tablet container in order to protect from light."*

The MAH committed to perform an in-use stability study for the 0.25 mg strength in 250 tablets container size for 4 months. The stability results show that the 0.25 mg tablets packaged in the largest container are stable during 20 weeks in-use conditions. The post-approval commitment has been resolved (see also page 11 Steps taken after the finalisation of the initial procedure).
The MAH committed to perform the in-use stability studies of the finished product packed in the HDPE containers at the controlled storage conditions. The stability results show that the 0.25, 1 and 4 mg tablets packaged in the HDPE container are stable during 8 weeks in-use conditions. The post-approval commitment has been resolved (see also page 11 Steps taken after the finalisation of the initial procedure).

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 Clinical aspects

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

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the Dutch reference product Risperdal.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Risperidon CF 1 mg tablet is compared with the pharmacokinetic profile of the reference product Risperdal 1 mg tablet.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution profiles of the Dutch and the German Risperdal 1 mg tablets. It is concluded that the use of the German reference product in the bioequivalence study is acceptable.
During the mutual recognition procedure Poland expressed a 'potential serious risk to public health' regarding the absence of comparitive dissolution profiles of all strenghts of the test product with the German and Polish reference product. For this reason, the MAH committed to submit results of dissolution profiles of Risperidon CF 0.25, 0.5, 1, 2, 3, 4, 6 and 8 mg tablets (test product) in comparison with the German reference product used in the bioequivalence study, Risperdal® 1 mg film-coated tablets (Janssen-Cilag GmbH, Germany) and in comparison with the Polish reference product Rispolept 1 mg film-coated tablets (Janssen Pharmaceutica N.V., Belgium). The national marketing authorization can not be granted in Poland unless the required dissolution profiles are provided. The dissolution data have been submitted and this post-approval commitment has been resolved (see also page 11 Steps taken after the finalisation of the initial procedure).

A single-dose, randomised, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 26 healthy male subjects (+ 2 alternates), aged 18-40 years. Each subject received a single dose (1 mg) of one of the 2 risperidone formulations. The tablet was orally administered with 240 ml water after 10 hours of fasting. For each subject there were 2 dosing periods, separated by a washout period of 14 days. Blood samples were collected at pre-dose and 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, and 192 hours after administration of the products. Two subjects were withdrawn from the study, because of personal reasons. The alternatives were chosen to replace them in the analysis. Twenty-six 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=26	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	35.8 ± 53.2	37.1 ± 54.8	5.3 ± 1.8	1.0 (0.75 – 2.0)	5.4 ± 8.1
Reference	37.4 ± 61.1	38.6 ± 62.6	5.2 ± 2.2	1.33 (0.5 – 2.0)	6.2 ± 10.6
***Ratio(90% CI)**	1.02 (0.91 – 1.13)	1.02 (0.92 – 1.13)	1.04 (0.93 – 1.15)	--	--
CV (%)	22.2%	21.3%	21.8%	--	--

$AUC_{0-\infty}$ 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 CF 1 mg tablet and the Risperdal 1 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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

The Risperidon CF 1 mg tablets can be considered dose proportional with the 0.25, 0.5, 2, 3, 4, 6 and 8 mg tablets in accordance to the NfG on Bioavailability and Bioequivalence, although small differences between the formulations exist. This conclusion is based on the facts that the formulations are manufactured by the same manufacturer, the qualitative composition of the different strengths is the same, the formulations contain low concentrations of the active substance (< 5%), and the ratio between the amounts of excipients is similar and the dissolution profiles are similar. The pharmacokinetics of risperidone are linear in the range 0.25-8 mg. Therefore, the results of the bioequivalence study performed with the 1 mg tablets therefore apply to the other strengths.

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 one round with 20 participants, and concerned a combined package leaflet for risperidone film-coated tablets and risperidone oral solution. The package leaflet has been adapted taking into account the results of the test. The adapted package leaflet will be tested by the MAH. The MAH committed to update both final reports of the readability test and to submit the results as soon as possible. After authorisation the data of an additional readability test was added which included data of 10 participants. the post-approval commitment has been resolved (see also page 11 Steps taken after the finalisation of the initial procedure).

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Risperidon CF 0.25, 0.5, 1, 2, 3, 4, 6 and 8 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Risperdal 0.5, 1, 2, 3, 4, 6 and 8 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 consistent with that of the reference product.

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 CF 0.25, 0.5, 1, 2, 3, 4, 6 and 8 mg film-coated tablets were authorised in the Netherlands on June 15th 2006 for the 1, 2, 3, 4, 6 and 8 mg strengths and August 23rd 2006 for the 0.25 and 0.5 mg strengths.

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 Risperidon CF with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on December 21st 2006.

A European harmonised birth date has been allocated (May 31st 2006) and subsequently the first data lock point for risperidone is May 2009. The first PSUR will cover the period from December 2006 to May 2009, after which the PSUR submission cyclus is 3 years.

The date for the first renewal will be: December 21st 2011.

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

<u>Quality active substance</u>
- The MAH committed to submit a type II variation to update the DMF.

<u>Quality medicinal product</u>
- The MAH committed to perform an in-use stability study for the 0.25 mg strength in 250 tablets container size for 4 months.
- The MAH committed to perform the in-use stability studies of the finished product packed in the HDPE containers at the controlled storage conditions.

<u>Clinical aspects</u>
- The MAH committed to submit results of dissolution profiles of Risperidon CF 0.25, 0.5, 1, 2, 3, 4, 6 and 8 mg tablets (test product) in comparison with the German reference product used in the bioequivalence study, Risperdal® 1 mg film-coated tablets (Janssen-Cilag GmbH, Germany) and in comparison with the Polish reference product Rispolept 1 mg film-coated tablets (Janssen Pharmaceutica N.V., Belgium). The national marketing authorization can not be granted in Poland unless the required dissolution profiles are provided.
- The MAH committed to update both final reports of the readability test and to submit the results as soon as possible.

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 the procedure	Approval/ non approval	Assessment report attached
The MAH committed to submit results of dissolution profiles of Risperidon CF 0.25, 0.5, 1, 2, 3, 4, 6 and 8 mg tablets (test product) in comparison with the German reference product used in the bioequivalence study, Risperdal® 1 mg film-coated tablets (Janssen-Cilag GmbH, Germany) and in comparison with the Polish reference product Rispolept 1 mg film-coated tablets (Janssen Pharmaceutica N.V., Belgium). The national marketing authorization can not be granted in Poland unless the required dissolution profiles are provided. The comparable dissolution data have been submitted by the MAH. The member states considered the post approval commitment fulfiled. Subsequently, marketing authorization was granted in Poland.	NL/H/0918/ 001-008/MR	Post-approval commitment	NA	NA	Approval	N
The MAH committed to update both final reports of the readability test and to submit the results as soon as possible. After authorisation data of an additional readability test was added which included data of 10 participants. On basis of the provided data, the member states considered this post-approval commitment fulfiled.	NL/H/0918/ 001-008/MR	Post-approval commitment	NA	NA	Approval	N
The MAH committed to perform an in-use stability study for the 0.25 mg strength in 250 tablets container size for 4 months. The stability results show that the 0.25 mg tablets packaged in the largest container are stable during 20 weeks in-use conditions. The post-approval commitment has been resolved.	NL/H/0961/ 001-008/MR	Post-approval commitment	7-5-2008	15-7-2008	Approval	N
The MAH committed to perform the in-use stability studies of the finished product packed in the HDPE containers at the controlled storage conditions and to forward the results as soon as available. The stability results show that the 0.25, 1 and 4 mg tablets packaged in the HDPE container are stable during 8 weeks in-use conditions. The post-approval commitment has been resolved.	NL/H/0918/ 001-008/MR	Post-approval commitment	7-5-2008	15-7-2008	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Including batch control/testing.	NL/H/0918/ 001-008/IA/ 001	IA	27-8-2007	10-9-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0918/ 001-008/IA/ 002	IA	27-8-2007	10-9-2007	Approval	N

Change of batch size of the finished product. Up to 10-fold compared to the original batch size approved for marketing authorisation.	NL/H/0918/ 001-008/IA/ 003	IA	27-8-2007	10-9-2007	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Including batch control/testing.	NL/H/0918/ 001-008/IA/ 004	IA	27-8-2007	10-9-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0918/ 001-008/IA/ 005	IA	27-8-2007	10-9-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0918/ 001-008/IA/ 006	IA	27-8-2007	10-9-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0918/ 001-008/IA/ 007	IA	27-8-2007	10-9-2007	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Including batch control/testing.	NL/H/0918/ 001-008/IA/ 008	IA	27-8-2007	10-9-2007	Approval	N
Change in the name of the medicinal product in the Netherlands.	NL/H/0918/ 001-008/IB/ 009	IB	27-8-2007	26-9-2007	Approval	N
Change in the name of the medicinal product in the CZ and SK.	NL/H/0918/ 001-008/IB/ 010	IB	27-8-2007	26-9-2007	Approval	N
Change of batch size of the finished product. Up to 10-fold compared to the original batch size approved for marketing authorisation.	NL/H/0918/ 002-004/IA/ 011	IA	31-10-2007	14-11-2007	Approval	N
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved.	NL/H/0918/ 001-008/IA/ 012	IA	31-10-2007	14-11-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0918/ 001-002/IA/ 013 & NL/H/0918/ 007/IA/ 013	IA	18-2-2007	3-3-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. All other manufacturing operations except batch release.	NL/H/0918/ 003-006/IB/ 014	IB	18-2-2008	19-3-2008	Approval	N
Change of batch size of the finished product. Up to 10-fold compared to the original batch size approved for marketing authorisation.	NL/H/0918/ 005-006/IA/ 015	IA	22-2-2008	7-3-2008	Approval	N