CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Risperidon drank Mylan 1 mg/ml, oral solution
Mylan 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/0942/001/DC
Registration number in the Netherlands: RVG 34630

22 July 2009

Pharmacotherapeutic group:	Antipsychotics
ATC code:	N05AX08
Route of administration:	oral
Therapeutic indication:	treatment of schizophrenia and moderate to severe manic episodes
Prescription status:	Prescription only
Date of authorisation in NL:	10 December 2007
Concerned Member States:	Decentralised procedure with BE, DE, ES, IT, PT, SI, UK
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 drank Mylan 1 mg/ml, oral solution, from Mylan B.V., the Netherlands. The date of authorisation in the Netherlands was 10 December 2007. The product is indicated for

- the treatment of schizophrenia.
- Maintenance treatment of clinical improvement in patients who responded to initial treatment with risperidone
- the treatment of moderate to severe manic episodes.

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

Risperidone is, in chemical terms, a benzoisoxazole derivative and therefore does not belong in the current class of antipsychotics.
Risperidone is a monoaminergic antagonist. It has a high affinity for serotonin 5-HT_2 and dopamine D_2 receptors. Risperidone also binds to α_1-adrenergic receptors and, with a lower affinity, to histamine H_1- and α_2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors.
Risperidone acts on positive symptoms, and appears to be associated with a potential effect on negative symptoms.

This application concerns a generic application claiming essential similarity with the innovator product Risperdal oral solution 1 mg/ml (NL RVG 19127) which has been registered in the Netherlands by Janssen-Cilag B.V., the Netherlands since 15 January 1996. In addition, reference is made to Risperdal oral solution 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 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. The CPMP Guidance on the Investigation of Bioavailability and Bioequivalence states that no bioequivalence study is required for an oral product, provided the excipients within it do not affect gastrointestinal transit time, absorption or *in vivo* stability of the active substance. Risperidon drank Mylan 1 mg/ml fulfills these requirements, and therefore a bioequivalence study is not requested for this application. However, the applicant has supported a bioequivalence study, which is considered as supportive. 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.

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 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

General
The active substance is risperidone, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white to almost white powder that is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol and dissolves in dilute acid solutions. The substance is polymorphic and form I is used.

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.

** 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.*

Manufacturing process
The CEP procedure was used and a copy of the most recent version was provided.

Specification
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 of several residual solvents as mentioned in the CEP. The specifications for known impurities and any other impurities are according to the EP, impurities A-E have been specified as such. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches. The MAH committed to provide batch analysis of three full scale productive batches of drug substance according to the current specifications.

Stability
The active substance is stable for 3 years when stored in double polyethylene bags in fibre drums. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition
Risperidon drank Mylan 1 mg/ml contains as active substance 1 mg of risperidone per ml, and is a clear and colourless solution.

The solution is packed in a Type III Amber glass bottle with a PP/LDPE plastic child-resistant and tamper-evident cap and a pipette wiper. Bottle sizes are 30 ml, 60 ml, 100 ml and 120 ml. A pipette (polystyrene plunger, LDPE barrel and piston) is also supplied. The graduation on the pipette is in milligrams and corresponding millilitres. The minimum volume is 0.25 ml. The maximum volume is 4 ml. Includes pipette holder: LDPE protective sheath for pipette. The pipette is in conformity with the pipette of the innovator.

The excipients are: tartaric acid (E334), benzoic acid (E210), dilute hydrochloric acid (for pH adjustment),

purified water.

Pharmaceutical development
The development of the product (oral solution) is based on the innovator product. The excipients used are common in the manufacture of this dosage form. The packaging materials are usual and suitable for the product at issue. The concentration of the preservative is adequate and justified given the concentration in the innovator product. In general, the development of the product is adequately performed and justified.

The excipients are all of Ph. Eur. quality. Certificates of analysis of all excipients have been included in the dossier and show compliance to the Ph. Eur. monographs.

Manufacturing process
The applied manufacturing process can be regarded as a standard process. Process validation data was presented for 2 pilot scale batches and a validation protocol for full scale bathes was included. The MAH committed to submit validation results on three production scale batches.

Microbiological attributes
The effectiveness of the preservative benzoic acid was tested according to the EP 5.1.3 requirements. Testing was done on three stability batches at release, at 15 months long-term storage conditions and at 6 months accelerated storage conditions. The proposed concentration of 1.5 mg/ml was found to be effective. A solution with a concentration of 0.15 mg/ml benzoic acid was also found to be effective. The applicant has chosen 1.5 mg/ml based on the innovator's product, which contains 2.0 mg/ml. The proposed concentration can be accepted.

Quality control of the medicinal product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, colour of the solution, pH, filling volume, identification (risperidone and benzoic acid), related substances, contents, microbiological purity and preservative efficacy. A specification for uniformity of mass of delivered doses is included.
Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Batch analytical data of one laboratory scale batch and two pilot scale batches from the proposed production site have been provided, demonstrating compliance with the specification. Satisfactory validation data for the analytical methods have been provided.

Stability tests on the finished product
Based on the submitted stability data (including in-use stability), a shelf-life of 24 months was granted. Full testing and bracketing design have been combined. Data on the smallest and largest pack size have been submitted up to 18 months. Data on the 100 ml pack has been submitted up to 24 months. The efficacy of the preservative has been determined at 29 months. The labelled storage conditions are *'Do not store above 30 ºC. Do not refrigerate or freeze. Store in the original package.'* The in-use period is 4 months.
The MAH committed to place the first 3 commercial scale batches on stability under long-term and accelerated storage conditions. The shelf life of the finished product has been changed from 2 into 3 years following a IB variation (NL/H/0942/001/IB/001).

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.

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.

Bioequivalence
According to the EMEA guideline on bioequivalence, a bioequivalence study is not required for this application of generic oral solution product. The product does not contain excipients which may interfere with absorption. However, for this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Risperidon drank Mylan 1 mg/ml is compared with the pharmacokinetic profile of the French reference product Risperdal oral solution 1 mg/ml, marketed by Janssen-Cilag. As no bioequivlaence study is required for this application, the study data were considered as supportive.

Risk management plan
Risperidone has been authorised in the EU for more than 10 years, 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 content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Risperdal drank 1 mg/ml marketed by Janssen-Cilag B.V., the Netherlands.
There is, however, a major difference; during the decentralised procedure the indication ‘treatment of severe aggression in patients with advanced forms of dementia’ was deleted from the SPC, as this indication could not be approved by all member states.
As at finalisation of the decentralised procedure an article 30 referral to harmonised the product information of the innovator product Risperdal was already pending, it was deemed acceptable by all member states involved. The MAH committed to harmonise the Product Information within 3 months after the end of the referral of Risperdal with this innovator SPC.

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 readability test was performed to justify the use of a readability test for Risperidon film coated tablets, which was performed by the same company, but for a different applicant for EU applications. This readability test for Risperidon film coated tablets has been approved by the Swedish authorities. A first pilot test was performed with 2 participants. One further test round of 10 test persons was performed (diagnostic and scoring). There were sufficient questions (23) about the critical sections including questions on comprehensibility and applicability also testing traceability as well as technical readability aspects.
Upon receipt of comments from the member states, a further test round with 5 participants was performed to demonstrate that the test patients could use and understand the instructions on how to use the product. The 5 participants also participated in the previous round. They were asked to perform a demonstration on how they would use this medicine and they were informed that their answers would be recorded in writing and that photographic images of their demonstration would be taken. All 5 test persons were able to use and understand the instructions. No revisions to the PIL were made.

The readability test resulted in 100% answers found in the first round and 99.1% correct answers. No revisions to the PIL were made.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Risperidon drank Mylan 1 mg/ml is a generic form of Risperdal oral solution 1 mg/ml. Risperdal oral solution 1 mg/ml is a well-known medicinal product with an established favourable efficacy and safety profile.

In accordance with the CPMP Guidance on the Investigation of Bioavailability and Bioequivalence no bioequivalence study is required for an oral solution product, provided the excipients used do not affect gastrointestinal transit time, absorption or *in vivo* stability of the active substance. However, the MAH submitted the results of one bioequivalence study, which were regarded as supportive data.

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 and are in agreement with other risperidone containing products.

The Board followed the advice of the assessors.

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 drank Mylan 1 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 18 September 2007. Risperidon drank Mylan 1 mg/ml was authorised in the Netherlands on 10 December 2007.

A European harmonised birth date has been allocated and subsequently the first data lock point for risperidone is 31 May 2009. The first PSUR will cover the period from September 2007 to May 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 18 September 2012.

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

<u>Quality - active substance</u>

- The MAH committed to provide batch analysis of three full scale productive batches of drug substance according to the current specifications if any results are found to be out of specification.

<u>Quality - medicinal product</u>

- The MAH committed to submit validation results on three production scale batches if any results are found to be out of specification.
- The MAH committed to place the first three commercial scale batches on stability under real time and accelerated conditions and to submit if any results are found to be out of specification.

<u>Product information</u>

- The MAH committed to harmonise the Product Information within 3 months after the end of the Art. 30 referral of Risperdal with this innovator SPC.

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
Change in the shelf life of the finished product from 2 into 3 years.	NL/H/0942/ 001/IB/001	IB	18-02-2008	19-03-2008	Approval	N
Change in the name of the Marketing Authorisation Holder	NL/H/0942/ 001/IA/002	IA	21-04-2008	05-05-2008	Approval	N
Change in the name of the medicinal product	NL/H/0942/ 001/IB/003	IB	21-04-2008	22-05-2008	Approval	N
Change in the name of a manufacturer responsible for batch release	NL/H/0942/ 001/IA/004	IA	21-04-2008	05-05-2008	Approval	N
To derogate from the obligation to show certain information on the labelling and the insert (Belgium only)	NL/H/0942/ 001/II/005	II	21-10-2008	25-11-2008	Approval	N
Change in the name and/or address of the marketing authorisation holder	NL/H/0942/ 001/IA/006	IA	29-10-2008	13-11-2008	Approval	N