CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Risperidon Accord 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, film-coated tablets
Accord Healthcare Ltd, United Kingdom

risperidone

EU-procedure number: NL/H/1078/001-006/DC
Registration number in the Netherlands: RVG 100170,100172-100176

26 November 2009

Pharmacotherapeutic group:	other 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:	8 September 2008
Concerned Member States:	Decentralised procedure with BE, DE, EE, ES, HU, IE, IT, LV, MT, PT, 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 Accord 0.5/1/2/3/4/6 mg, film-coated tablets, from Accord Healthcare Ltd. The date of authorisation was on 8 September 2008 in the Netherlands.

The product is indicated for:

- treatment of schizophrenia.
- 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.

The last two indications are part of approved SPC after type-II variation NL/H/1078/001-006/II/001.

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

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Risperdal 0.5, 1, 2, 3, 4, 6, 8 mg film-coated tablets (NL RVG 22714/16096/16097/ 16098/16099/19585 and 19586, respectively), which has been registered in the Netherlands by Janssen-Cilag since 1994 (1, 2, 3 and 4 mg), 1998 (6 mg and 8 mg) and 1999 (0.5 mg). Risperdal 8 mg has been withdrawn from the Netherlands on 31 December 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.

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 1 mg tablet, registered in the United Kingdom. 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 products.

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 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.*). The drug substance is a white or almost white powder. It is freely soluble in methylene chloride, sparingly soluble in ethanol, and practically insoluble in water. The substance shows polymorphism.

Manufacture
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.

Specification
Specifications for the drug substance are according to the Ph.Eur. Several additional specifications have been noted on the CEP. The MAH has also included specifications for microbial quality and particle size. Batch analysis data showing compliance with the drug substance specification have been provided for six production scale batches.

Stability
A re-test period of 36 months when stored in double polyethylene bags in HDPE drums is noted on the CEP.

* *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.*

Medicinal Product

Composition
Risperidon Accord 0.5 mg contains as active substance 0.5 mg of risperidone, and is a brick red coloured, round, biconvex, film-coated tablet, plain on both sides.
Risperidon Accord 1 mg contains as active substance 1 mg of risperidone, and is a white to off white, capsule shaped, biconvex film-coated tablet, plain on both sides.
Risperidon Accord 2 mg contains as active substance 2 mg of risperidone, and is a light orange coloured, capsule shaped, biconvex film-coated tablet, plain on both sides.
Risperidon Accord 3 mg contains as active substance 3 mg of risperidone, and is a light yellow coloured, oval shaped, biconvex film-coated tablet with a break line on one side and plain on other side.
Risperidon Accord 4 mg contains as active substance 4 mg of risperidone, and is a green coloured, capsule shaped, biconvex film-coated tablet, plain on both sides.

Risperidon Accord 6 mg contains as active substance 6 mg of risperidone, and is a yellow coloured, round, biconvex film-coated tablet, plain on both sides.

The film-coated tablets are packed in PVC/PVdC/Al blisters of 20, 28, 30, 50, 60, 90, 100 and 120 tablets.

The excipients are:

Tablet core:
lactose monohydrate, maize starch, cellulose microcrystalline (E460), sodium laurilsulfate, colloidal anhydrous, silica (E551), purified talc (E553b), magnesium stearate (E572).

Tablet coating:
0.5 mg: hypromellose (E464), propylene glycol (E1520), titanium dioxide (E171), purified talc (E553b), ferric oxide red (E172)
1 mg: hypromellose (E464), propylene glycol (E1520), purified talc (E553b)
2 mg: hypromellose (E464), propylene glycol (E1520), titanium dioxide (E171), purified talc (E553b), Lake of Sunset yellow (E110)
3 mg: hypromellose (E464), propylene glycol (E1520), titanium dioxide (E171), purified talc (E553b), Lake of quinoline yellow (E104)
4 mg: hypromellose (E464), propylene glycol (E1520), purified talc (E553b), titanium dioxide (E171), Lake of quinoline yellow (E104), Lake of indigo carmine (E132)
6 mg: hypromellose (E464), propylene glycol (E1520), titanium dioxide (E171), purified talc (E553b), Lake of quinoline yellow (E104), Lake of sunset yellow (E110)

Pharmaceutical development
The development of the immediate release tablet has been satisfactorily performed. The excipients used are common in the manufacturing of film-coated tablets. The packaging materials are usual and suitable for the product at issue. The tablet strengths are not all dose proportional and several formulations have been tested. The tablets are distinguishable by colour of the coating and the shape of the tablets.

The excipients comply with the Ph.Eur., except for the colouring agents (E104, E110 and E132, in-house specifications) and the iron oxide red (USP). Specifications of the iron oxide and the other colouring agents have been provided. The specifications are acceptable.

Manufacturing process
The drug product is manufactured in a wet granulation, drying, compression and film-coating process. Adequate in-process controls have been implemented. The manufacturing process should be considered a non-standard process for the 0.5, 1, 2, 3 and 4 mg products as they contain ≤ 2% active substance. The manufacturing process has been adequately validated using production scale batches. The 0,5 mg and 1 mg formulations are fully dose proportional as are the 2 mg and 3 mg formulations. The 1mg, 2 mg, 4 mg and 6 mg formulations contains the same amount of excipients, i.e. the sum of lactose + active drug was kept constant.

Product specification
The drug product specification includes tests for description, average tablet weight, uniformity of mass, uniformity of dosage units, loss on drying, disintegration time, identification (risperidone and colouring agents), related substances, assay, dissolution and microbial purity. The 3 mg tablets are also tested for breakability (uniformity of mass or content) as they contain a break-mark. The analytical methods have been adequately described and validated. Batch analysis data from the proposed production site have been provided on three pilot scale size batches of each strength, demonstrating compliance with the release specification.

Stability tests on the finished product
Stability data have been obtained during storage at 25 ºC/60% RH for up to 24 months, at 30 ºC/65% RH for up to 12 months and at 40 ºC/75% RH for up to 6 months. The drug products were packaged in the proposed commercial package, i.e. clear PVC/PVDC-Aluminium blisters. Photostability data show

adequate protection properties of the packaging material. Several out of specifications of impurities were observed at accelerated conditions. Based on the stability data, the proposed shelf-life of 24 months can be granted for all products. The additional storage condition *'Do not store above 30 ºC'* has been adopted. The MAH committed to place at least one batch each year under stability studies and to include the first three commercial scale batches of each tablet strength in the stability program.

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.

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

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results of the innovator product marketed in the Netherlands and the United Kingdom.

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

Study design
A single-dose, two-way crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18-55 years. Each subject received a single dose (1 mg) of one of the 2 risperidone formulations. The tablet was orally administered with 240 ml of water. There were 2 dosing periods, separated by a washout period of 9-14 days. Blood samples were collected pre-dose and at 0.16, 0.33, 0.5, 0.67, 0.83, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96 and 120 hours after administration of the products.
Data of 46 subjects were available for statistical analyses. One subject was excluded because of nausea, and the other because of fever (not treatment related).

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

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

Treatment N=46	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	36.6 ± 33.4	38.0 ± 34.5	5.4 ± 2.5	1.8 ± 0.9 (0.67-5)	-
Reference	38.7 ± 38.7	40.2 ± 40.1	6.1 ± 2.9	1.5 ± 0.5 (0.67-2.5)	-
***Ratio (90% CI)**	0.98 (0.92-1.05)	0.98 (0.92-1.05)	0.90 (0.82-0.97)	-	-
CV (%)	19.9	19.4	24.4	-	-

$AUC_{0-\infty}$ 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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 9-OH-risperidone under fasted conditions.

Treatment N=46	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	106.7 ± 40.8	112.1 ± 41.1	4.4 ± 2.0	5 (2.5-10)	-
Reference	108.8 ± 39.1	113.7 ±38.8	4.5 ± 1.9	4 (1-8)	-
*Ratio (90% CI)	0.97 (0.90-1.04)	0.97 (0.91-1.04)	0.96 (0.89-1.03)	-	-
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*

Results

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 9-OH-risperidone under fasted conditions, it can be concluded that Risperidon Accord 1 mg film-coated tablets and Risperdal 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.

Some tablet strengths are dose proportional to the 1 mg tablet that was used in the bioequivalence study, but other tablets were dose similar (i.e. the sum of lactose + active drug was kept constant). As the active compound contributes for less than 5% to the total tablet weight, the dissolution profile of all strengths is rapid and comparable to 1 mg tablet and the manufacturing site is the same, a biowaiver to other strengths is acceptable. In conclusion, the results of the study with the 1 mg formulation can be extrapolated to the other strengths (0.5, 2, 3, 4 and 6 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 has been authorised in the EU for more than 10 years. 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. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Pharmacovigilance

There were three remaining points for clarification, which have to be solved post-approval. See post-approval commitments on page 6. Provided that these deficiencies are rectified prior to placing the medicinal product on the market, the Pharmacovigilance system will fulfil the requirements. The MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

Product information

SPC

The SPC was adapted during the procedure and was found acceptable. The MAH committed to update the product information according to the final outcome of the article 30 referral procedure for the innovator product Risperdal.

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 two rounds with 10 participants each. Fourteen questions were asked. In the first round at least 90% scored well on the diagnostic questions. Therefore no changes were made to the leaflet for the second test round. Results of the second round of testing confirmed the results of the first round. At least 90% of the respondents scored well on the diagnostic questions. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Risperidon Accord 0.5/1/2/3/4/6 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Risperdal film-coated tablets. Risperdal film-coated tablets 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. However, there are three remaining points for clarification, which have to be resolved post-approval (see below).

The SPC, package leaflet and labelling are in the agreed templates and are in general agreement with other risperidone containing products. The product information will be updated in accordance with the outcome of the article 30 referral for the innovator Risperdal.

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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Risperidon Accord 0.5/1/2/3/4/6 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 July 2008. Risperidon Accord 0.5/1/2/3/4/6 mg, film-coated tablets were authorised in the Netherlands on 8 September 2008.

The MAH will submit PSURs in accordance with the data lock point of the innovator product Risperdal (31 May 2009). The first PSUR will cover the period from July 2008 to 31 May 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 February 2013.

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

Quality - medicinal product

- The MAH committed to place at least one batch each year under stability studies and to include the first three commercial scale batches of each tablet strength in the stability program.

Pharmacovigilance system

- The MAH committed to document the following activities in SOPs before the products are placed on the market or before September 2008, whichever is earlier.
  1) Risk management
  2) Benefit/risk assessment
  3) Notifying competent authorities of changes to the benefit/risk balance of products
  4) Meeting commitments to competent authorities
  5) Medical enquiries
  6) Interaction between safety issues and product defects
  7) Handling of urgent safety restrictions and safety variations
  8) Management and use of the safety database and internal audit of the PVS
  9) Electronic reporting
- The MAH committed to have a validated data base in place before the product is placed on the market.
- The MAH committed to have the Quality Management System in place before the product is placed on the market.

  These commitments have been fulfilled.

Product information

- The MAH committed to update the product information in accordance with the final outcome of the article 30 referral procedure for the innovator product Risperdal.
  This commitment has been fulfilled (see variation NL/H/1078/001-006/II/001 on page 11).

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
Harmonisation SPC and PIL	NL/H/1078/ 001-006/ II/001	II	1-6-2009	11-7-2009	Approval	N
Change in pack size of the finished product; additional pack size of 20 tablets.	NL/H/1078/ 003-006/ IB/002	IB	9-9-2009	12-10-2009	Approval	N
Change in pack size of the finished product; additional pack sizes of 50 tablets and 100 tablets per carton.	NL/H/1078/ 001-006/ IA/003	IA	9-9-2009	23-9-2009	Approval	N