CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Mirtazapine Ratiopharm dispersible 15/30/45 mg, orodispersible tablets
Ratiopharm GmbH, Germany

mirtazapine

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/1103/001-003/MR
Registration number in the Netherlands: RVG 34984-6

25 August 2009

Pharmacotherapeutic group:	other antidepressants
ATC code:	N06AX11
Route of administration:	oral
Therapeutic indication:	major depressive episode
Prescription status:	prescription only
Date of first authorisation in NL:	1 March 2007
Concerned Member States:	Mutual recognition procedure with AT, DE, LU, NO, PT, SE, UK (all strenghts) BE, ES, LT, (only 15 mg) IT (only 30 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 Mirtazapine Ratiopharm dispersible 15/30/45 mg, orodispersible tablets, from Ratiopharm GmbH. The date of authorisation was on 1 March 2007 in the Netherlands. The product is indicated for treatment of major depressive episode.

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

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S (+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R (-) enantiomer by blocking 5-HT_3 receptors.
Mirtazapine is also a histamine H1 receptor antagonist. This explains its sedative effect. It has practically no anticholinergic activity. At therapeutic doses, mirtazapine has practically no effect on the cardiovascular system.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Remeron SolTab orodispersible tablets 15/30/45 mg (NL RVG 25780, 25781 and 25781, respectively) which has been registered in the Netherlands by Organon since 2001 (original product). In addition, reference is made to Remeron SolTab and Zispin SolTab 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 Zispin SolTab 45 mg orodispersible tablets, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference product.

No new 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.

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 drug substance mirtazapine is described in the Ph.Eur*. The drug substance is a white to almost white powder, slightly hygroscopic to hygroscopic. There is a chiral centre and the substance exists as a racemic mixture. Two polymorphic forms exist, an anhydrous crystalline form and a hemihydrate crystalline form. Mirtazapine contains a chiral center but is manufactured as a racemate.

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.

Manufacture
A reaction scheme and a flow chart have been provided. The synthesis consists of four stages. Every stage has been described in sufficient detail. Various in-process controls are performed during the different manufacturing stages. Several reprocessing steps are described. No new solvents or reagents are used. It is indicated that R&D may recommend other processing steps. It has been noted that these new procedures should be submitted as a variation to the authorities. The DMF-holder declares that till date no reprocessing has been performed.

Specification
The drug substance specification is in line with the Ph.Eur., with additional requirements. The specification is acceptable in view of the route of synthesis and the various ICH guidelines. Batch analytical data demonstrating compliance with this specification have been provided for 3 consecutive production scale batches.

Stability
Stability data have been obtained during storage of 3 batches at 25ºC/60% RH and 40ºC/75% RH. The drug substance was packaged in the proposed packaging. The solid drug substance is stable with respect to degradation. No significant changes are observed during the 48 months period of normal storage conditions and 6 months accelerated storage conditions.
Based on the data provided, the recommended retest period of 36 months is justified.

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

Medicinal Product

Composition
Mirtazapine orodispersible tablets are white, round tablets debossed with “36” (15 mg) “37”(30 mg) or “38” (45 mg) on one side and ‘A’ on the other side with an embossed circular edge. The tablets are packed in PVC /polyamide/ aluminium/ polyester perforated unit dose blisters.
The excipients are: crospovidone (type B), mannitol (E421), cellulose, microcrystalline (E460), aspartame (E951), silica, colloidal anhydrous, magnesium stearate (E572), strawberry guarana flavor [maltodextrin, propylene glycol, artificial flavors, acetic acid (<1%)], and peppermint flavor [artificial flavors, corn starch].

Pharmaceutical development
The development of the product is satisfactorily performed and explained. The three strengths are dose proportional. The excipients used are common for tablets. The dissolution profiles of two test batches of each strength of Mirtazapine Ratiopharm orodispersible tablets were compared with the same strength reference product (Zispin SolTab). Comparative dissolution profiles over a 30 minutes period are presented, all recorded in a 900 ml 0.1 N HCl solution with 50 rpm paddle speed. The higher the strength the smaller the difference in dissolution between the Mirtazapine Ratiopharm orodispersible tablets and the reference product. It can be concluded that the tablets rapidly dissolve, in all cases at least 80% is dissolved after 5 minutes.

Manufacturing process
The products are established pharmaceutical forms and its development is adequately described in accordance with the relevant European guidelines.
The process is validated on 2 batches at the pilot production scale. A validation protocol for commercial production scale is presented.

Excipients
Except for the flavouring agents, which are controlled by in-house standards, all excipients are controlled in accordance with the corresponding Ph.Eur. monographs. For the specifications for the flavouring agents the MAH has adopted the specifications set by the supplier. In addition to the suppliers specification the MAH has included microbial limits and a particle size specification for the strawberry guarana flavour.

Product specification
Adequate dissolution specifications have been set. Additionally the product specification includes tests for identification and assay of Mirtazapine, appearance, uniformity of dosage, water content, related substances and microbial quality. Compound A is the major degradation product. The requirements for the degradation products are acceptable in view of the relevant ICH Guideline and the results of the stability studies. Batch analysis results of 2 batches from each strength have been provided. Compliance with the release requirements has been demonstrated.

Stability tests on the finished product
Data of stability studies performed at 30ºC/60% RH and 40ºC/75% RH have been submitted that justify the shelf-life of 2 years with no specific storage condition. The tablets show a slight increase in amount of compound A. However, the requirement was easily met. The tablets should be stored in the original PVC-Al/Al blister pack.

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 Remeron SolTab, 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 mirtazapine 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

Mirtazapine 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 Mirtazapine Ratiopharm dispersible 45 mg orodispersible tablets (Ratiopharm GmbH, Germany) is compared with the pharmacokinetic profile of the British reference product Zispin SolTab 45 mg orodispersibel tablets (Organon, UK).

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of the UK and NL originator products, and the dissolution profiles of reference products in different member states. The dissolution profiles of all concerned member states have been included.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

An open label, randomised, two treatment, two sequence, two period, cross-over, single dose comparative oral bioequivalence study was carried out under fasted conditions in 24 (+4 alternates) healthy male volunteers, aged 20-41 years. Each subject received a single dose (45 mg) of one of the 2 mirtazapine formulations. After a 10 hour fasting period, the tablet was placed directly on to the subject's tongue. Subjects were instructed to leave the tablet on the tongue for 60 seconds without crushing or breaking the tablet with teeth or spitting. After 60 seconds the subjects had to swallow everything first, before taking 240 ml of water. For each subject there were 2 dosing periods, separated by a washout period of 12 days.
Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours after administration of the products.
Four subjects were withdrawn: 3 subjects for positive testing of drug abuse on the check-in day of period II, and one subject because of vomiting. These subjects were replaced by an alternative. According to the protocol 24 subjects were eligible for pharmacokinetic analysis.

The method of measuring plasma samples and the statistical methods used were adequate.

Mirtazapine may be taken without reference to food intake, and It should be taken preferably as a single night-time dose before going to bed.. From the literature it is known that food does not interact with the absorption of mirtazapine. 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.

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

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1678 ± 513	1781 ± 547	126 ± 55	1.33 (0.67 – 6.0)	25 ± 8
Reference	1599 ± 519	1708 ± 565	128 ± 60	1.33 (0.67 – 6.0)	28 ± 9
***Ratio (90% CI)**	1.05 (0.96 - 1.14)	1.04 (0.96 - 1.13)	1.00 (0.91 – 1.10)	---	---
CV (%)	16.5	15.9	18.6	---	---

$AUC_{0-\infty}$ 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 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 mirtazapine under fasted conditions, it can be concluded that Mirtazapine Ratiopharm 45 mg and the reference Zispin SolTab 45 mg are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 15 and 30 mg orodispersible tablet formulations are composed of the same granula as the 45 mg formulation. The qualitative composition of the granula and the ratio between the amounts of active substance and excipients is the same for the 3 orodispersible tablet formulations. In addition, it is known that mirtazapine shows linear pharmacokinetics. Therefore, the results obtained for the 45 mg formulation can be extrapolated to the 15 and 30 mg formulations.

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

Mirtazapine was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of mirtazapine 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 is similar to the SPC as approved for Mirtazepine Merck, DK/H/986/001-003/DC and DK/H/989/001-003/DC during a decentralised procedure in which various countries were involved.

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 PIL tested is not identical to the PIL submitted with this application. However, the MAH has submitted a bridging statement in which was mentioned that the sections for indications, contra-indications, warnings, other safety-information and side effects are identical. Also, the MAH has stated that the key messages for safe use of the product have been similarly addressed in both the user tested and nationally approved PIL. This argumentation is endorsed by the RMS.
Two cohorts of 10 participants were interviewed. After the first round of 10 participants, some amendments were made to the Leaflet. Two amendments concerned the deletion/modification of a standard sentence from the QRD template (in section Pregnancy and lactation and Interactions) which is not considered to be acceptable. In the PIL submitted with these MRP-applications, those standard sentence has not been amended/deleted.
Diagnostic testing was performed. Questions (15 in total) were asked about all parts of the leaflet. Each question was divided into 2 subquestions. In the first subquestion, it was asked where some information could be found. In the second subquestion, the participants were asked to answer a question about the information in this part of the text.
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

Mirtazapine Ratiopharm dispersible 15/30/45 mg, orodispersible tablets have a proven chemical-pharmaceutical quality and are generic forms of Remeron SolTab orodispersible tablets. Remeron SolTab 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 similar to the SPC as approved for Mirtazepine Merck, DK/H/986/001-003/DC and DK/H/989/001-003/DC during a decentralised procedure in which various countries were involved. The text of sections 4.4 and 4.8 has been updated according to PhVWP recommendations (see commitment, and variation NL/H/1103/001-003/IB/011 in “steps taken after finalisation of the initial procedure” table).

The Board followed the advice of the assessors. Mirtazapine Ratiopharm was authorised in the Netherlands on 1 March 2007.

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 Mirtazapine Ratiopharm 15/30/45 mg orodispersible tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 25 January 2008.

A European harmonised birth date has been allocated (1 September 1994) and subsequently the first data lock point for mirtazapine is September 2010. The first PSUR will cover the period from January 2008 to September 2010. Thereafter, the PSUR submission cycle is 3 years.

The date for the first renewal will be: 25 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 commercial scale batches of Mirtazapine Ratiopharm 15mg/30mg/45mg orodispersible tablets manufactured by complete conversion into individual strength whenever these batches are manufactured based on commercial requirements. This commitment has been fulfilled by variation NL/H/1103/001-003/MR, see “steps taken after finalisation of the initial procedure”.
- The MAH has committed to place samples from the first three full-scale commercial batches of Mirtazapine Ratiopharm orodispersible 15/30/45 mg tablets resulting from full conversion of the blend batch size into individual strengths on stability. This commitment has been fulfilled by variation NL/H/1103/001-003/MR, see “steps taken after finalisation of the initial procedure”.

Product information

- The MAH has committed to update/harmonize the product information according to the outcome of the article 30 referral for the innovator product Remeron, which was still ongoing at the closing of the procedure. This commitment has been fulfilled by variation NL/H/1103/001-003/IB/011, see “steps taken after finalisation of the initial procedure”.

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 to batch release arrangements and quality control testing of the finished product. Replacement or addition of a site where batch control/testing takes place.	NL/H/1103/ 001-003/IA/ 001	IA	26-3-2008	9-4-2008	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. Not including batch control/testing. Addition of a manufacturer responsible for batch release.	NL/H/1103/ 001-003/IA/ 002	IA	26-3-2008	9-4-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/1103/ 001-003/IA/ 003	IA	26-3-2008	9-4-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms. Replacement or addition of a manufacturing site for secondary packaging.	NL/H/1103/ 001-003/IA/ 004	IA	26-3-2008	9-4-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms. Replacement or addition of a manufacturing site for secondary packaging.	NL/H/1103/ 001-003/IA/ 005	IA	26-3-2008	9-4-2008	Approval	N
Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules etc.) in a pack. Change within the range of the currently approved pack sizes.	NL/H/1103/ 001-003/IA/ 006	IA	26-3-2008	9-4-2008	Approval	N
Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules etc.) in a pack. Change outside the range of the currently approved pack sizes.	NL/H/1103/ 001-003/IB/ 007	IB	31-3-2008	29-4-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/1103/ 002/IA/008	IA	31-3-2008	14-4-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the active substance. From a manufacturer currently approved.	NL/H/1103/ 001-003/IA/ 009	IA	17-6-2008	1-7-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the	NL/H/1103/ 001-002/IA/ 010	IA	16-10-2008	30-10-2008	Approval	N

finished product. Secondary packaging site for all types of pharmaceutical forms.						
Validation of first three commercial scale batches for the maximum batch size. Batches have been placed on stability. Out of specification results will be reported.	NL/H/1103/ 001-003/ MR	Post-approval commitment	---	18-11-2008	Approval	N
Following the Decision issued by the European Commission on 15 September 2008 concerning the referral under Article 30 of Directive 2001/83/EC of Remeron and associated names, 15, 30 and 45 mg tablets, 15, 30 and 45 mg orodispersible tablets, 15 mg/ml oral solution, the SPC/PIL of generic Mirtazapine was updated accordingly.	NL/H/1103/ 001-003/IB/ 011	IB	18-2-2009	20-3-2009	Approval	N