

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Mirtazapine Pfizer 15 mg, 30 mg and 45 mg,
orodispersible tablets
Pfizer B.V., the Netherlands**

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/1966/001-003/MR
Registration number in the Netherlands: RVG 105823, 105825-105826**

25 August 2010

Pharmacotherapeutic group:	other antidepressants
ATC code:	N06AX11
Route of administration:	oral
Therapeutic indication:	major depressive episodes
Prescription status:	prescription only
Date of first authorisation in NL:	7 September 2009
Concerned Member States:	Mutual recognition procedure with AT, CZ, ES, FR, HU, IE, IT, RO, 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 Mirtazapine Pfizer 15 mg, 30 mg and 45 mg, orodispersible tablets from Pfizer B.V. The date of authorisation was on 7 September 2009 in the Netherlands. The product is indicated for treatment of major depressive episodes.

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-HT₁ receptors, because 5-HT₂ and 5-HT₃ 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-HT₂ receptors and the R(-) enantiomer by blocking 5-HT₃ receptors.

The histamine H₁-antagonistic activity of mirtazapine is associated with its sedative properties. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Remeron SolTab 15 mg, 30 mg and 45 mg orodispersible tablets (NL License RVG 25780-25782), which have been registered since 11 June 2001 by N.V. Organon. Reference is also made to the innovator products Remeron 15 mg, 30 mg and 45 mg film-coated tablets (NL License RVG 16685, 16686 and 18127), which have been registered in the Netherlands since 16 March 1994 (15 and 30 mg) and 16 January 1995 (45 mg). In addition, reference is made to Remeron authorisations in the individual member states.

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 active substance is mirtazapine, an established active substance described in the European Pharmacopoeia (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 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 suitability 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.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur, with additional requirements for residual solvents, particle size and microbial purity. The specification is acceptable in view of the route of synthesis and the various ICH guidelines. Batch analysis data of fourteen batches have been provided. All batch results comply with the complete set of specifications.

Stability of drug substance

A retest period of 36 months has been granted, when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

* *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

Mirtazapine Pfizer 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 Polyamide/Aluminium/PVC/Paper/Polyster/Aluminium perforated unit dose blisters.

The excipients are: crospovidone (type B), mannitol (E421), microcrystalline cellulose (E460), aspartame (E951), colloidal anhydrous silica, magnesium stearate, strawberry guarana flavour [maltodextrin, propylene glycol, artificial flavours, acetic acid (<1%)], peppermint flavour [artificial flavours, corn starch].

The three strengths are dose proportional.

Pharmaceutical development

The development of the product is satisfactorily performed and explained. The excipients used are common for tablets. The dissolution profiles of two test batches of each strength 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 Pfizer 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 manufactured in a standard process. A flow diagram has been provided. The process includes sifting, drying, granulation, blending/lubrication and compression.

Sufficient process validation data have been presented on two pilot-scale batches and three production-scale batches of each strength.

Control of 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.

Quality control of drug product

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 two pilot-scale batches and three commercial-scale batches of each strength have been provided. Compliance with the release requirements has been demonstrated.

Stability of drug product

Data of stability studies performed at 30°C/70% RH and 40°C/75% RH have been submitted that justify the shelf-life of 3 years with no specific storage condition. The tablets show a slight increase in amount of compound A. However, the requirement was easily met.

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 orodispersible tablets, which are 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 a bioequivalence study in which the pharmacokinetic profile of the test product Mirtazapine Pfizer 45 mg (Pfizer B.V., NL) is compared with the pharmacokinetic profile of the reference product Zispin SolTab 45 mg orodispersible tablets (Organon, UK).

The choice of the reference product

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.

Design

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.

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.

Results

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.

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

Treatment N=24	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	1678 \pm 513	1781 \pm 547	126 \pm 55	1.33 (0.67 – 6.0)	25 \pm 8
Reference	1599 \pm 519	1708 \pm 565	128 \pm 60	1.33 (0.67 – 6.0)	28 \pm 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-∞} 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					

**In-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 Pfizer 45 mg and 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.

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.

Extrapolation to different strengths

The 15 and 30 mg orodispersible tablet formulations are composed of the same granulations as the 45 mg formulation. The qualitative composition of the granulations 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 post authorisation 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 for the innovator Remeron has been harmonised through an article 30 referral in 2008. The SPC Mirtazapine Pfizer is fully in accordance with this harmonised text.

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 sentences have 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 Pfizer 15 mg, 30 mg and 45 mg, orodispersible tablets have a proven chemical-pharmaceutical quality and are generic forms of Remeron SolTab 15 mg, 30 mg and 45 mg 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 consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Mirtazapine Pfizer 15 mg, 30 mg and 45 mg, orodispersible tablets were authorised in the Netherlands on 7 September 2009.

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 Pfizer 15 mg, 30 mg and 45 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 22 July 2010.

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 until September 2010. Thereafter, the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 May 2014.

There were no post-approval commitments made during the 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 _{1/2}	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