CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Mirtazapine 15, 30 and 45 mg orodispersible tablets Sandoz 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/713/001-003/DC
Registration number in the Netherlands: RVG 33366-8

29 September 2009

Pharmacotherapeutic group:	other antidepressants
ATC code:	N06AX11
Route of administration:	oral
Therapeutic indication:	major depressive episode
Prescription status:	prescription only
Date of authorisation in NL:	23 July 2007
Concerned Member States:	Decentralised procedure with CZ, DE, ES, HU, SK (all strengths), EE, LT, LV (only 15 mg and 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 15, 30 and 45 mg orodispersible tablets, from Sandoz B.V. The date of authorisation was on 23 July 2007 in the Netherlands. The product is indicated for major depressive episode.

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

Mirtazapine is a centrally active presynaptic α2 receptor antagonist, which increases noradrenergic and serotoninergic neurotransmission. The enhancement of serotoninergic 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 the α2 and 5-HT2 receptors and the R(-) enantiomer by blocking the 5-HT3 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 decentralised 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 authorisations in the individual member states (reference product).

In Lithuania the application for the 15 mg and the 30 mg strength was withdrawn before the start of the procedure (21 March 2007).

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 Remeron SolTab orodispersible tablets, registered in the Netherlands. 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. 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, 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 an established active substance described in the Ph.Eur. The active substance is a white to creamy white powder that is practically insoluble in water, and freely soluble in toluene, methanol, ethanol, acetone, and isopropanol. The solubility in aqueous solution is pH dependent. Mirtazapine exists as an anhydrate and as a hemihydrate. In this drug product the hemihydrate form is used. 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
Mirtazapine is prepared via a three-step synthesis and subsequent purification and crystallization. The solvents used in the purification crystallisation steps determine whether the hemihydrate or the anhydrate is formed. The quality of the starting materials has been adequately described in the ASMF.
The drug substance has been sufficiently characterized. In general sufficient information has been provided on the synthesis. Also, for the starting material and solvents acceptable specifications have been adopted.

Specification
The drug substance specification will meet both requirements of USP and Ph.Eur., with additional requirements for residual solvents. The specification is acceptable in view of the route of synthesis and the various ICH guidelines. The proposed limit for di-isopropylether has been further tightened to 560 ppm. This limit is imposed for adoption in the Drug Substance specification.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full-scale batches.

Stability
Stability data of 3 pilot batches have been obtained during storage at 25°C/60%RH and 40°C/75%RH. The drug substance was adequately stored. The solid drug substance is stable with respect to degradation, but seems sensitive to light (decolouration). Additional photostability data will be forwarded as soon as available. The MAH also committed to provide stability results of production scaled batches stored during 24 months storage at 25°C/60% RH in due course. Based on the data provided, the recommended retest period of 24 months, when stored in the original package, 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
The product is formulated as an orodispersible tablet. The product will be marketed in three different strengths 15 mg, 30 mg, and 45 mg. The three different strengths are fully dose proportional. According to the SPC the maximum dose of the product is 45 mg/day.

The drug product is packaged into aluminium blister packs. The packaging is usual for this type of dosage form.

The excipients are: mannitol (E421), povidone K30, crospovidone, silica colloidal anhydrous, aspartame (E951), calcium stearate, orange flavour [maltodextrin, natural and artificial flavourings, dl-alpha-tocopherol], peppermint flavour [maltodextrin, natural flavourings, dextrin, sulphites].

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation differs from the innovator's reference product. The products are considered essentially similar with the innovator product based upon the dissolution and impurity profiles.

Manufacturing process
The drug product is prepared by conventional wet granulation process followed by compression. Purified water is used as granulation fluid. The various steps of the manufacturing process, the process parameters, and the in-process controls have been sufficiently described. And the process was adequately validated with 2 full scaled batches and 1 pilot batch of each tablet strength.

Excipients
The excipients comply with Ph.Eur. except for the flavouring substances, which are not described in any pharmacopoeia. The specifications for the excipients are acceptable.

Product specification
The product specification includes tests for appearance, identity, odour, uniformity of content, disintegration time, loss on drying, resistance to crushing, assay, degradation, dissolution and microbiological quality.
The release requirements are acceptable, the proposed end of shelf-life limits for some parameters can be tightened. The MAH has made a commitment to perform a re-evaluation of the limits for degradation products, resistance to crushing, and dissolution rate when more stability data becomes available.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 2 full scaled batches and 1 pilot batch of each tablet strength, demonstrating compliance with the release specification.

Stability tests on the finished product
The drug product has been stored at 25°C/60%RH, 30°C/65%RH, and 40°C/75%RH. When stored at 25°C and 30°C up to three months, results of 2 full scaled batches and 1 pilot batch of each tablet strength show an increase in the disintegration time. Thereafter no change in this parameter is seen. All other examined parameters remain stable. When stored at 40°C/75%RH a significant increase in one of the individual impurities is observed, therefore the addition of a storage condition, do not store above 30°C is justified. On the basis of the submitted stability data a shelf-life of 21 months, do not store above 30°C, store in the original container, can be granted. On 16 April 2008 the shelf life was extended to 24 months by a type IB variation (NL/H/713/001-003/IB/007). Subsequently, on 15 November 2008 the shelf life was changed to 36 months (NL/H/713/001-003/IB/012).

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 application does not contain non-clinical data, which is acceptable for this generic application, because the pharmacological and toxicological properties of mirtazapine are well known and no new preclinical data are available. The MAH has provided a non-clinical overview in which the pharmacological, toxicological and pharmacokinetic properties of the active substance have been adequately described. The overview gives a good review of the data published in open literature. Given the experience with the innovator product Remeron SolTab, orodispersible tablets in the Netherlands and in the EU, registration can be granted from a preclinical point of view.

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 30 mg orodispersible tablets is compared with the pharmacokinetic profile of the reference product Remeron Soltab 30 mg orodispersible tablets.

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

*Bioequivalence study 1: tablets administered **with** water*
A randomised, open label, two-treatment, two-period, two-sequence, single-dose cross-over bioequivalence study was carried out under fasted conditions in 32 (30 + 2 alternates) healthy male subjects, aged 18 to 40 years. The biostudy was performed blinded with regard to the sequence of the product administration. Each subject received a single dose (30 mg) of one of the 2 mirtazapine formulations with 240 ml water. The tablet was placed on the subjects tongue until it disintegrates or up to a maximum of 1 minute. Subjects were instructed to take 2 or 3 mouthful of water with swirling so that if any drug particulate left over in the mouth cavity will be ingested followed by intake of the remaining quantity of the 240 ml water. The tablets were administered after an overnight fast. Fasting was continued for 4 hrs after dosing. For each subject there were 2 dosing periods, separated by a washout period of 22 days. Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours after administration of the products.
One subject was withdrawn from the study because of adverse events. This subject was replaced by an alternative receiving Test and Reference in the same order. According to the protocol 30 subjects were eligible for pharmacokinetic analysis.
The method of measuring plasma samples and the statistical methods used were adequate.

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

Treatment N=30	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	905 ± 216	967 ± 231	70 ± 18	2.00 (1.0 – 4.0)	26 ± 8
Reference	948 ± 207	1008 ± 232	68 ± 17	2.33 (1.0 – 4.0)	25 ± 7
***Ratio (90% CI)**	0.95 (0.91 - 0.99)	0.96 (0.92 - 1.00)	1.02 (0.95 – 1.10)	---	---
CV (%)	9.5	8.9	15.6	---	---

$AUC_{0-\infty}$ 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*

According to the SPC the tablet should be put on the tongue until disintegrated. Water or other liquid is not needed to swallow the dose. Although it can be argued that the study design may not be the most critical design as water was taken after disintegration of the tablet, the RMS finds the current design adequate to compare both formulations. In case no water is used to swallow the tablet, it can be put forward that the outcome it also dependent on the subject's ability to swallow similarly in both study periods and in addition to produce enough and similar amounts of saliva in both periods.

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. The RMS concluded that based on the pharmacokinetic parameters of mirtazapine under fasted conditions Mirtazapine 30 mg and Remeron SolTab 30 mg are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

However, during the decentralised procedure, an objection was raised by one CMS with regard to the dosing posology, in which it is stated that the orodispersible tablets can be taken with or without water. As bioequivalence was only proven after intake of water, bioequivalence should have been demonstrated without administration of water. Bioequivalence has to be demonstrated in the different methods of administration to assure interchangeability with innovator products and with other generics. Otherwise interchangeability could be a potential serious risk to public health. To resolve this issue, the MAH was requested to perform a new bioequivalence study without water to be submitted as a type II variation post-approval (see Annex I).

The 15 and 45 mg orodispersible tablet formulations are dose proportional to the 30 mg formulation. The qualitative composition and the ratio between the amounts of active substance and excipients is the same for the 3 orodispersible tablet formulations. The tablets are manufactured by the same manufacturer and the same manufacturing process. In addition, it is known that mirtazapine shows linear pharmacokinetics within the recommended dose range. Therefore, the results obtained for the 30 mg formulation can be extrapolated to the 15 and 45 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

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. Before the actual readability test commenced, a so called “Audience Design Step” was performed. In this Step, an “Expert Patient” (person treated for depression in the past and thus, experienced with leaflets of antidepressants) critically read the leaflet in order to refine the contents and design of the leaflet. For instance, language in the leaflet was simplified. The questionnaire was developed by determining the 15 most important points of information relating to specific safety and compliance issues. A sufficient number of questions have been developed testing “traceability”, “comprehension” and “applicability”, i.e. can the patient find the information quickly and easily, can he/she understand it and act on it appropriately. The questionnaire was tested in pilot interviews and was found not to raise problems. Two cohorts of 10 participants of sufficiently diverse demographic and sociologic criteria were recruited. Appropriate individual demographic and sociologic details were provided and the way of recruitment was presented.

The test results were presented for the complete number of participants and not for each cohort. Apparently, the PIL successfully passed in the first cohort of 10 persons and no changes in the PIL were needed. The user test showed that the leaflet enabled 90% of participants to find, and 90% of those to express in their own words each piece of information tested. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Mirtazapine 15, 30 and 45 mg orodispersible tablets have a proven chemical-pharmaceutical quality and are a generic form 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 between Mirtazapine 30 mg tablets and the 30 mg Remerson SolTab in a bioequivalence study with administration with water in compliance with the requirements of European guidance documents. However, during the decentralised procedure, an objection was raised with regard to the dosing posology, in which it is stated that the orodispersible tablets can be taken with or without water. To resolve this issue, the MAH was requested to perform a new bioequivalence study without water to be submitted as a type II variation post-approval (see Annex I).

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other mirtazapine containing products. However, adaptation of section 4.4 and 4.8 of the SPC and section 2 of the PIL were included according to PhVWP recommendations for antidepressants and suicidal thoughts and behaviour (see annex 2).

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 Mirtazapine with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 March 2007. Mirtazapine was authorised in the Netherlands on 23 July 2007.

A European harmonised birth date has been allocated (1 September 1994). The PSUR submission cycle is 3 years. The first data lock point for mirtazapine is September 2010. The first PSUR will cover the period from October 2004 to September 2007.

The date for the first renewal will be: 1 June 2011.

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

<u>Quality - active substance</u>
- The MAH has committed to forward additional photostability data as soon as available.
- The MAH committed to provide stability results of production scaled batches stored during 24 months storage at 25°C/60% RH.

<u>Quality - medicinal product</u>
- The MAH has committed to perform a re-evaluation of the limits for degradation products, resistance to crushing, and dissolution rate when more stability data becomes available.
- The MAH has committed to submit samples of Mirtazapine tablets to the United Kingdom.
- The MAH committed to provide additional certificates of analysis for production scaled batches.

<u>Clinical</u>
- The MAH committed to perform a new bioequivalence study without water to be submitted as a type II variation (see Annex I).

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
SGOT	serum glutamic oxaloacetic transaminase
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 finshed product. Replacement or addition of a manufacturer responsible for batch release, including batch control/testing.	NL/H/713/001-003/IA/001	IA	22-8-2007	5-9-2007	Approval	N
Change in the batch size of the finished product. Up to ten-fold of the original batch size approved at the granting of the marketing authorization.	NL/H/713/001-003/IA/002	IA	29-8-2007	12-9-2007	Approval	N
Change in the name of the medicinal product.	NL/H/713/001-003/IB/003	IB	22-8-2007	21-9-2007	Approval	N
Submission of new bioequivalence study. Tablets administered without water.	NL/H/713/001-003/II/004	II	25-8-2007	25-10-2007	Approval	Y, Annex I
Withdrawal of the marketing authorization in Estonia on 8 February 2008.	NL/H/713/001-002/DC	Withdrawal	---	8-2-2008	---	N
Change in the name of the medicinal product.	NL/H/713/001-003/IB/005	IB	17-3-2008	16-4-2008	Approval	N
Change in batch size of active substance or intermediate. Up to ten-fold compared to the original batch size approved at the grant of the marketing authorization.	NL/H/713/001-003/IA/006	IA	4-3-2008	25-4-2008	Non - Approval	N
Change in the shelf-lfe of the finished product as packaged for sale	NL/H/713/001-003/IB/007	IB	17-3-2008	16-4-2008	Approval	N
Minor change in the manifacturing process of the active substance.	NL/H/713/001-003/IB/008	IB	17-3-2008	6-3-2008	Withdrawn	N
Change in the name of the medicinal product.	NL/H/713/001-003/IB/009	IB	17-3-2008	16-4-2008	Approval	N
Type II amendements of SPC and PIL for antidepressants.	NL/H/713/001-003/II/010	II	18-3-2008	2-4-2008	Approval	N
Update of DMF.	NL/H/713/001-003/II/011	II	31-5-2008	9-12-2008	Approval	N
Change in the shelf-life of the finished product as packaged for sale. Based on updated 36 months long term stability data, there will be an extension of shelf life from 24 months to 36 months.	NL/H/713/001-003/IB/012	IB	16-10-2008	15-11-2008	Approval	N
Change in the SPC of an essentially similar product 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 (EMEA/CHMP/500252/2008). The MAH has updated the SPC/PIL accordingly.	NL/H/713/001-003/IB/013	IB	18-2-2009	6-4-2009	Approval	Y, Annex II

Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance. A minor change in the test for related substances for the active substance Mirtazapin.	NL/H/713/001-003/IA/014	IA	26-8-2009	9-9-2009	Approval	N

ANNEX I to the PAR

POST-approval commitment – Fasted bioequivalence study: tablets administered without water

For this post-approval commitment, the MAH submitted one bioequivalence study in which the pharmacokinetic profile of the test product Mirtazapine 30 mg (Sandoz B.V., the Netherlands) is compared with the reference product Remeron Soltab 30 mg (Organon, The Netherlands) under fasted conditions and without water. During the decentralised procedure, an objection was raised by one CMS with regard to the dosing posology, in which it is stated that the orodispersible tablets can be taken with or without water. As bioequivalence was only proven after intake of water, bioequivalence should have been demonstrated without administration of water. Bioequivalence has to be demonstrated in the different methods of administration to assure interchangeability with innovator products and with other generics. Otherwise interchangeability could be a potential serious risk to public health. To resolve this issue, the MAH has submitted the following bioequivalence study by a post-approval type II variation.

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).

The reference product is considered acceptable. The batch size of the test tablet is in line with the guidelines, in which a batch size is requested of at least 100.000 tablets and over 1/10th of the commercial batch size. The same test product is used in the first study in which the tablets were administered with water.

A randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 32 (30 + 2 alternates) healthy male subjects, aged 19 to 35 years. Each subject received a single dose (30 mg) of one of the 2 mirtazapine formulations. The tablet was placed on the subject's tongue, where it disintegrated rapidly and was swallowed with saliva. No water was administered for taking the tablet. The tablets were administered after an overnight fast and fasting was continued for 4 hrs after dosing. For each subject there were 2 dosing periods, separated by a washout period of 21 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, 16, 24, 48, 72, 96, 120, and 144 hours after administration of the products.
One subject did not check in for the second period, two subjects were withdrawn prior period II because of elevated SGOT and bilirubin levels, and two subjects had 4 consecutive time points missing in Period II and I. These subjects were excluded from analysis. Twenty-seven subjects were eligible for pharmacokinetic analysis.

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

Treatment N=27	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1005 ± 322	1043 ± 360	68.3 ± 23.6	2.0 (0.67 – 4.0)	27 ± 10
Reference	1055 ± 357	1099 ± 389	72.1 ± 24.1	2.67 (1.33 – 4.0)	28 ± 10
***Ratio (90% CI)**	0.96 (0.89 – 1.04)	0.96 (0.88 – 1.04)	0.96 (0.85 – 1.07)	---	---
CV (%)	16.9	16.9	25.3	---	---

$AUC_{0-\infty}$ 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 and administered without water, it can be concluded that Mirtazapine 30 mg and Remeron SolTab 30 mg are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence has been shown between the Mirtazapine 30 mg tablets and the 30 mg Reference product, both after administration without water as well as after administration with water. Therefore the orodispersible tablet can be taken with and without water, analogous to the situation for the reference product.

Conclusion

Based on the review of the data of the bioequivalence study under fasted conditions in which the tablets were administrated without water, the concerned member states considered the post-approval commitment for Mirtazapine 15, 30 and 45 mg orodispersible tablets, fulfilled. The findings of the two bioequivalence studies support the current recommendations of the SPC that the test product can be taken with or without water. The SPC does not need any adjustments.

Annex II to the PAR

Type II variation - Antidepressants and suicidal thoughts and behaviour.

Adaptation of section 4.4 and 4.8 of the SPC and section 2 of the PIL to PhVWP recommendations for antidepressants and suicidal thoughts and behaviour.

Section 4.4 - Special Warnings and Special Precautions for Use

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Mirtazapine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders
Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Section 4.8
Where reports of suicidal thoughts or behaviour have been reported with a particular product, this should be reflected in section 4.8

Where a table of adverse drug reactions (ADRs) is included in this section, suicidal ideation and suicidal behaviour should be included in this table – frequency not known and include the following as a footnote:

“Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation (see section 4.4).”

Where no table of ADRs is included the above text should be inserted in this section.

Revised wording for the Patient Information Leaflet

Thoughts of suicide and worsening of your depression or anxiety disorder
If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this:

- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, **contact your doctor or go to a hospital straight away.**
You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.