IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Mirap DisTab 15 mg Orodispersible Tablets
Mirtazapine
PA0711/094/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number NL/H/0712/001-003 with the Netherlands as RMS. The responsibility of RMS was transferred to Ireland on19 July 2023 under procedure number IE/H/1300/001-003
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0711/094/001-003
Marketing Authorisation Holder: Rowex Ltd.

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The NL public assessment report published at the time of the initial marketing authorisation is provided herein.

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).

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. QUALITY ASPECTS

Compliancewith Good ManufacturingPractice

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,BPare officialhandbooks(pharmacopoeias)inwhich methodsof 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.

Stabilitytests 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 29 March 2008 the shelf life was extended to 24 months by a type IB variation (NL/H/711/001-003/IB/006). Subsequently, on 15 November 2008 the shelf life was changed to 36 months (NL/H/711/001-003/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.

III. 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

IV. 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, tmax (median, range)) of mirtazapine under fasted conditions, administered with water.

Treatment N=30	**AUC0-t ng.h/ml**	**AUC0-∞ ng.h/ml**	**Cmax ng/ml**	**tmax h**	**t1/2 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	---	---

AUC0-∞ area under the plasma concentration-time curve from time zero to infinity
AUC0-t area under the plasma concentration-time curve from time zero to t hours
Cmax maximum plasma concentration
tmax time for maximum concentration
t1/2 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 AUC0-t, AUC0-∞ and Cmax 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.

V. OVERALL CONCLUSIONS

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: Quality-active substance
- 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.

Quality- medicinal product
- 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.

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

VI. REVISION DATE

25 April 2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From NL/H/0712/001-003 to IE/H/1300/001-003	N/A	19 July 2023	N/A