Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Mirtazapine 15 mg film-coated tablets
Mirtazapine 30 mg film-coated tablets
Mirtazapine 45 mg film-coated tablets

mirtazapine

PL 14251/0296-0298

Manx Healthcare Limited

LAY SUMMARY

Mirtazapine 15 mg, 30 mg and 45 mg film-coated tablets
mirtazapine

This is a summary of the Public Assessment Report (PAR) for Mirtazapine 15 mg, 30 mg and 45 mg film-coated tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Mirtazapine tablets in this lay summary for ease of reading.

For practical information about using Mirtazapine tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Mirtazapine tablets and what are they used for?
These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Mirtazapine 15 mg, 30 mg and 45 mg film-coated tablets (PL 00065/0144-45 & 0157). The reference medicine used in the bioequivalence study was Remeron 30 mg film-coated tablets.

Mirtazapine tablets are used to treat depressive illness in adults.

How do Mirtazapine tablets work?
These medicines contain the active ingredient mirtazapine, which is one of a group of medicines called antidepressants.

How are Mirtazapine tablets used?
The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (by mouth).

The recommended starting dose is 15 or 30 mg every day. The patient's doctor may advise the patient to increase their dose after a few days to the amount that is best for the patient (between 15 and 45 mg per day). The dose is usually the same for all ages. However, if the patient is elderly or if they have renal or liver disease, the patient's doctor may adapt the dose.

For further information on how Mirtazapine tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Mirtazapine tablets have been shown in studies?
Because Mirtazapine tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two

medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Mirtazapine tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Mirtazapine tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Why were Mirtazapine tablets approved?
It was concluded that, Mirtazapine tablets has been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Mirtazapine tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Mirtazapine tablets. The RMP details the important risks of Mirtazapine tablets, how these risks can be minimised, any uncertainties about Mirtazapine tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Mirtazapine tablets:

List of important risks and missing information	
Important identified risks	QT prolongation and/or ventricular arrhythmia (e.g. Torsades de Pointes)
Important potential risks	None
Missing information	None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Mirtazapine tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Mirtazapine tablets

Marketing authorisations for Mirtazapine tablets were granted in the United Kingdom (UK) on 04 September 2024.

The full PAR for Mirtazapine tablets follows this summary.

This summary was last updated in November 2024.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Mirtazapine 15 mg, 30 mg and 45 mg film-coated tablets (PL 14251/0296-0298) could be approved.

The products are approved for the following indication:
In adults for the treatment of episodes of major depression.

Mirtazapine is a centrally active presynaptic α2-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 α2 and 5-HT2 receptors and the R(-) enantiomer by blocking 5-HT3 receptors.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Mirtazapine 15 mg, 30 mg and 45 mg film-coated tablets (PL 00065/0144-45 & 0157) that have been licensed for a suitable time, in line with the legal requirements.

The reference medicine used in the bioequivalence study was Remeron 30 mg film-coated tablets.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations for Mirtazapine 15 mg, 30 mg and 45 mg film-coated tablets were granted in the United Kingdom (UK) on 04 September 2024.

II QUALITY ASPECTS

II.1 Introduction

These products consist of film-coated tablets, containing 15 mg, 30 mg or 45 mg of the active substance mirtazapine.

In addition to mirtazapine, these products also contain the following excipients:
Tablet core
Lactose monohydrate
Maize starch
Hydroxypropylcellulose
Colloidal anhydrous silica
Magnesium stearate

Tablet coating 15 mg strength
Opadry II, Yellow, 03F520551 containing:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Iron oxide yellow (E172)

Tablet coating 30 mg strength
Opadry II, Beige 03F570104 containing:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Iron oxide yellow (E172)
Iron oxide red (E172)

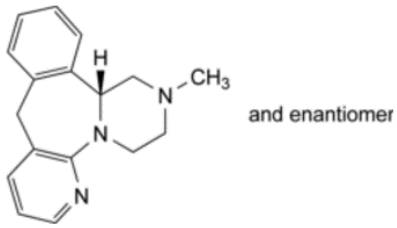
Tablet coating 45 mg strength
Opadry II, White (3F180011) containing:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)

The finished products are packaged in a white opaque PVC/PVDC/aluminium blister, in a pack size of 28 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: Mirtazapine
Chemical Name: (14bRS)-2-Methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1-a]pyrido[2,3-c][2]benzazepine.
Molecular Formula: $C_{17}H_{19}N_3$
Chemical Structure:



Molecular Weight: 265.4
Appearance: White or almost white powder, slightly hygroscopic to hygroscopic.
Solubility: Practically insoluble in water, freely soluble in anhydrous ethanol.

Mirtazapine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of mirtazapine are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of mirtazapine are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study.

This study was an open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study, comparing the test product Mirtazapine 30 mg film-coated tablets, versus the reference product, Remeron 30 mg film-coated tablets, in healthy, adult, human subjects under fasted conditions.

After an overnight fast of at least 10 hours, subjects were administered one tablet of test or reference product with 240 ml ± 2 ml of water. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 21 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 40)			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
C_{max} (ng/mL)	53.903	54.915	98.16	18.95	91.45% - 105.36%	99.96
AUC_{0-t} (hr*ng/mL)	662.055	685.112	96.63	13.29	91.93% - 101.58%	100.00

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional (15 mg and 45 mg) strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 30 mg product strength can be extrapolated to the other strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations was recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with mirtazapine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**