

Public Assessment Report

Scientific discussion

Mirtazapine Bluefish

(mirtazapine)

SE/H/2384/01-03/DC

This module reflects the scientific discussion for the approval of Mirtazapine Bluefish. The procedure was finalised at 2024-03-05. For information on changes after this date please refer to the module ‘Steps taken after the finalisation of the initial procedure - Summary’.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Mirtazapine Bluefish, 15 mg, 30 mg, 45 mg, Film-coated tablet.

The active substance is mirtazapine. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

harmacotherapeutic group: other antidepressants, ATC code: N06AX11

Mode of action

Mirtazapine is a centrally active presynaptic $\alpha_2\alpha_2$ -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 $\alpha_2\alpha_2$ and 5-HT₂ receptors and the R(-) enantiomer by blocking 5-HT₃ receptors.

Claimed indication and posology

For the treatment of episodes of major depression in adults.

The effective daily dose is usually between 15 and 45 mg; the starting dose is 15 or 30 mg.

Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

It is recommended to discontinue treatment with mirtazapine gradually to avoid withdrawal symptoms.

II.2 General comments on the submitted dossier

The application for Mirtazapine Bluefish, 15 mg, 30 mg, 45 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IE and PL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Remeron, 15 mg, film-coated tablet authorised in NL since 1994, with N.V. Organon as marketing authorisation holder.

The reference product used in the bioequivalence study is Remeron, 30 mg, film-coated tablet from NL with N.V. Organon as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP

The clinical study site and the bioanalytical facility were inspected by the Spanish authority (AEMPS) in 2019 and the inspection team judged that the corrective and preventative actions were adequate. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of mirtazapine are well known. As mirtazapine is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

Since Mirtazapine Bluefish is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Mirtazapine Bluefish from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Mirtazapine, 30 mg, film-coated tablets, with the reference product Remeron, 30 mg, film-coated tablets.

Pharmacokinetic properties of the active substance

Absorption: Mirtazapine has an oral bioavailability of ~50 %. Following oral administration, maximal plasma concentrations occur at approximately 2 hours.

The pharmacokinetics of mirtazapine is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of mirtazapine is linear within the dose range 15 mg – 80 mg.

Elimination: The terminal half-life is 20-40 hours.

Study 023-21, 30 mg - FASTING

Methods

This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Mirtazapine, 30 mg, film-coated tablets with Remeron, 30 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 96 hours post-dose. Plasma concentrations of mirtazapine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max} . The study was conducted between 2021-08-06 and 2021-11-16.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range) for mirtazapine, n=36.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	816.987 ± 283.041	68.437 ± 26.393	1.50 (0.750-4.000)
Reference	846.605$\pm$ 309.698	68.249 ± 24.583	1.50 (0.750-3.670)
*Ratio (90% CI)	97.04 (92.45-101.87)	100.54 (92.24-109.59)	-
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 plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 15 mg and 45 mg.

Discussion and overall conclusion

Based on the submitted bioequivalence study, Mirtazapine Bluefish (mirtazapine), 30 mg, film-coated tablets is considered bioequivalent with Remeron, 30 mg, film-coated tablets.

The results of study 023-21 with 30 mg formulation CAN be extrapolated to other strengths 15 mg and 45 mg, according to conditions in the Guideline on the investigation of Bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1, section 4.1.6.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Mirtazapine Bluefish.

Part II Safety specification

The MAH has submitted the version 0.2 RMP dated 2023-10-05 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	QT prolongation and/or ventricular arrhythmia (e.g. Torsades de Pointes)
Important potential risks	None
Missing information	None

Assessor's comment: The proposed Summary of safety concerns is in line with the CMDh list of safety concerns published for Mirtazapine Aurobindo. The assessor agrees that the safety concerns listed by the MAH are appropriate.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP

Summary of the RMP is considered acceptable.

Conclusion of RMP assessment

The submitted Risk Management Plan, version 0.2 signed 2023-10-05 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date

The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Mirtazapine Bluefish, is found adequate. There are no objections to approval of Mirtazapine Bluefish, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Mirtazapine Sandoz 15, 30 and 45 mg orodispersible tablets, regarding content and Venlafaxine 37.5mg, 75mg and 150mg Capsules (MAH: Bluefish Pharmaceuticals) regarding layout.

The bridging report submitted by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-