

# Public Assessment Report Scientific discussion

## Mirtazapin Newbury (mirtazapine)

**This module reflects the scientific discussion for the approval of Mirtazapin Newbury. The procedure was finalised at 2025-10-14. For information on changes after this date please refer to the module 'Update'.**

## TABLE OF CONTENTS

<b>I.</b>	<b>Introduction</b>	<b>3</b>
<b>II.</b>	<b>Executive summary</b>	<b>3</b>
<b>II.1</b>	<b>About the product</b>	<b>3</b>
<b>II.2</b>	<b>General comments on the submitted dossier</b>	<b>3</b>
<b>II.3</b>	<b>General comments on compliance with GMP, GLP, GCP and agreed ethical principles</b>	<b>3</b>
<b>III.</b>	<b>Scientific OVERVIEW AND DISCUSSION</b>	<b>4</b>
<b>III.1</b>	<b>Quality aspects</b>	<b>4</b>
<b>III.2</b>	<b>Non-clinical aspects</b>	<b>4</b>
<b>III.3</b>	<b>Clinical aspects</b>	<b>5</b>
<b>IV.</b>	<b>BENEFIT RISK ASSESSMENT</b>	<b>8</b>
<b>V.</b>	<b>RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION</b>	<b>8</b>
<b>V.1</b>	<b>List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC</b>	<b>8</b>
<b>V.2</b>	<b>List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC</b>	<b>8</b>
<b>V.3</b>	<b>Summary of Product Characteristics (SmPC)</b>	<b>9</b>
<b>V.4</b>	<b>Package Leaflet (PL)</b>	<b>9</b>
<b>V.4.1</b>	<b>Package Leaflet</b>	<b>9</b>
<b>V.4.2</b>	<b>Assessment of User Testing</b>	<b>9</b>
<b>VI.</b>	<b>STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY</b>	<b>10</b>

## **I. INTRODUCTION**

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Mirtazapin Newbury, 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**

Pharmacotherapeutic group: other antidepressants, ATC code: N06AX11

#### Mechanism of action

Mirtazapine is a centrally active presynaptic  $\alpha_2$ -antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT<sub>1</sub> receptors, because 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking  $\alpha_2$  and 5-HT<sub>2</sub> receptors and the R(-) enantiomer by blocking 5-HT<sub>3</sub> receptors.

#### Claimed indication

Mirtazapine is indicated in adults for the treatment of episodes of major depression.

### **II.2 General comments on the submitted dossier**

The application for Mirtazapin Newbury, 15 mg, 30 mg, 45 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

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 Sweden since 1996, with NV Organon as marketing authorisation holder.

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

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

The MPA 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 within the European Community, the MPA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the European Community, the MPA 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. The QP-declaration is acceptable.

GCP

A statement on the application of appropriate GCP standards in the submitted study has been provided.

No issues regarding GCP have been identified. Inspection reports from inspections by multiple authorities (WHO, USFDA; MHRA, AGES/EMA) during the period 2019-2023 have been reviewed. Based on this review, the clinical and the analytical facility utilized are considered to have acceptable verified quality systems for the period around when the study in question was performed. 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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

### **Environmental Risk Assessment (ERA)**

The Applicant commits to submit an updated ERA in line with the 2024 ERA guideline by variation application within 4 years of the date of this letter. A formal letter of commitment has been provided. This is acceptable.

### **Overall conclusions**

Pharmacodynamic, pharmacokinetic and toxicological properties of mirtazapine are well known, and the provided information is acceptable. The Applicant commits to submit updated ERA within 4 years; commitment letter has been provided.

There are no remaining concerns from a non-clinical perspective.

## **III.3 Clinical aspects**

### **Pharmacokinetics**

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Mirtazapine with the reference product Remeron.

#### Pharmacokinetic properties of the active substance

*Absorption:* Mirtazapine has an oral bioavailability of about 50 %. Following an oral dose of mirtazapine 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 recommended dose range.

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

#### Study 21-VIN-0164

##### *Methods*

This was a single-dose, two-way crossover study conducted in 44 healthy volunteers, comparing Mirtazapine, 30 mg, tablets with Remeron, 30 mg, tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 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  $AUC_{0-72h}$  and  $C_{max}$ . The study was conducted between 2021-08-23 and 2021-09-17.

##### *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=40.**

<b>Treatment</b>	<b>AUC<sub>0-72h</sub></b> ng*h/ml	<b>C<sub>max</sub></b> ng/ml	<b>t<sub>max</sub></b> h
<b>Test</b>	<b>699 <math>\pm</math> 235</b>	<b>58.8 <math>\pm</math> 29.1</b>	<b>2.00</b> <b>(0.50 - 4.00)</b>
<b>Reference</b>	<b>721 <math>\pm</math> 247</b>	<b>58.8 <math>\pm</math> 22.6</b>	<b>2.17</b> <b>(0.75 - 4.00)</b>
<b>*Ratio (90% CI)</b>	<b>96.63</b> <b>(91.93 - 101.58)</b>	<b>98.16</b> <b>(91.45 - 105.36)</b>	<b>-</b>
AUC <sub>0-72h</sub> area under the plasma concentration-time curve from time zero to 72 hours C <sub>max</sub> maximum plasma concentration t <sub>max</sub> time for maximum plasma concentration			

*\*calculated based on ln-transformed data*

For AUC<sub>0-72h</sub> and C<sub>max</sub> 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

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Mirtazapine Newbury is considered bioequivalent with Remeron.

Absence of studies with the additional strengths of 15 mg and 45 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled, since the pharmacokinetics of mirtazapine is linear within the recommended dose range and since mirtazapine is highly soluble. The Bioequivalence Guideline is applicable for this application according to Considerations regarding the implementation of ICH M13A on bioequivalence for immediate-release solid oral dosage forms (EMA/531548/2024), as the procedure for this application started 2024-11-12. Thus, selection of a lower strength for the bioequivalence study is acceptable.

#### **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**

##### Proposed MAH: Newbury Pharmaceuticals AB

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 MPA 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 Mirtazapin Newbury.

### Part II Safety specification

The MAH has submitted the version 0.1 RMP dated 01/10/2024 and proposed the following summary safety concerns:

<b>Summary of safety concerns</b>	
Important identified risks	<ul style="list-style-type: none"><li>• QT prolongation and/or ventricular arrhythmia (e.g. Torsades de Pointes)</li></ul>
Important potential risks	<ul style="list-style-type: none"><li>• None</li></ul>
Missing information	<ul style="list-style-type: none"><li>• None</li></ul>

The safety concerns listed by the MAH are appropriate. It is in line with the summary of safety concerns for other recently approved mirazapine medicinal products.

### 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

The Summary of the RMP is endorsed.

### Conclusion RMP assessment

The submitted Risk Management Plan, version 0.1 signed 01/10/2024 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.

**Renewal date**

The renewal date will be 5 years after approval date.

#### **IV. BENEFIT RISK ASSESSMENT**

The quality of the generic product, Mirtazapin Newbury, is found adequate. There are no objections to approval of Mirtazapin Newbury, 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 ratio is considered positive, and the application is therefore recommended for approval.

The applicant has committed to submit a variation according to section VI.2.

#### **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**

**Post approval commitments**

<b>Description</b>	<b>Due date</b>
Newbury Pharmaceuticals AB commits to submit an updated Environmental Risk Assessment (ERA) by variation application, within 4 years of the date of the commitment letter.	19 September 2029

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

- **Additional risk minimisation measures (including educational material)**

N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

N/A

### **V.3 Summary of Product Characteristics (SmPC)**

The approved SmPC is available on the Swedish MPA website.>

### **V.4 Package Leaflet (PL)**

#### **V.4.1 Package Leaflet**

The approved PL is available on the Swedish MPA website.

#### **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) 15mg, 30 mg, 45 mg orodispersible tablets, NL/H/0712/001-003 (current procedure number IE/H/1300/001-003), regarding content and Varenicline Newbury, 0.5 mg, 1 mg, film-coated tablets, SE/H/2196/01-03/DC, 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
-	-	-	-	-	-