LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Mirtazapine Grindeks
# (mirtazapine)

# SE/H/2418/01/DC

**This module reflects the scientific discussion for the approval of Mirtazapine Grindeks. The procedure was finalised on 2025-07-09. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Mirtazapine Grindeks, 15 mg, 30 mg, 45 mg, orodispersible tablet.

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

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Mirtazapine Grindeks, 15 mg, 30 mg, 45 mg, orodispersible tablet, is a generic article 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, NO, PL, PT and SI as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Remeron-S, 45 mg, orodispersible tablet, authorised in NO since 2002, with N.V. Organon as marketing authorisation holder.

The reference product used in the bioequivalence study is Remeron-S, 45 mg, orodispersible tablet, from NO with N.V. Organon as marketing authorisation holder.

**European Reference Product (ERP)**
For the applied strength 15 mg a European Reference Product is used in CMS AT, BG, CZ, DK, EE, EL, FI, HR, HU, LT, LV, PL and SI: Remeron-S, 15 mg, orodispersible tablet, authorised in NO since 2002, with N.V. Organon as marketing authorisation holder.
For the applied strength 30 mg a European Reference Product is used in CMS AT, BG, CZ, DK, EE, EL, FI, HR, LT, LV, PL and SI: Remeron-S, 30 mg, orodispersible tablet, authorised in NO since 2002, with N.V. Organon as marketing authorisation holder.
For the applied strength 45 mg a European Reference Product is used in CMS AT, BG, CZ, DK, EE, EL, ES, FI, HU, LT, LV, PL and SI: Remeron-S, 45 mg, orodispersible tablet, authorised in NO since 2002, with N.V. Organon as marketing authorisation holder.

The justification to use this product is based on information received from NO. The ERP information was circulated during the validation period.

**Potential similarity with orphan medicinal products**
N/A

# II. QUALITY ASPECTS

## II.1 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.

### II.2 Medicinal 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. 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 provided a Phase I ERA with the conclusion: […] In addition, this application concerns a generic product according to Article 10(1). Therefore, the marketing of this medicinal product will not represent the release of an additional quantity of mirtazapine to the environment, since it will only substitute a percentage of existing reference product usage without leading to an increased consumption. Consequently, no experimental environmental risk assessment is deemed necessary for this application.

Since Mirtazapine Grindeks 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 Grindeks from a non-clinical point of view.

## IV. CLINICAL ASPECTS

**Pharmacokinetics**
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Mirtazapine Grindeks with the reference product Remeron-S.

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:* Mirtazapine displays linear pharmacokinetics within the recommended dose range.

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

Study MIR.45/405

*Methods*

This was a single-dose, two-way crossover study conducted in 38 healthy volunteers (34 completed), comparing Mirtazapine, 45 mg, orally disintegrating tablets with Remeron-S, 45 mg, orally disintegrating tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of R-mirtazapine and S-mirtazapine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for $AUC_{0-72}$ and $C_{max}$. The study was conducted between 2023-02-14 and 2023-03-20.

*Results*

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

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for R-mirtazapine, n=34.**

| Treatment | $AUC_{0-72}$ ng*h/ml | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **556.86 ± 205.612** | **47.94 ± 21.704** | **1.63 (1.00-4.50)** |
| **Reference** | **551.87 ± 194.108** | **48.41 ± 18.393** | **1.75 (1.00-4.50)** |
| ***Ratio (90% CI)** | **98.85 (89.16-109.59)** | **95.20 (82.61-109.71)** | **-** |
| **$AUC_{0-72}$** area under the plasma concentration-time curve from time zero to 72 hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum plasma concentration | | | |

**calculated based on ln-transformed data*

**Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for S-mirtazapine, n=34.**

| Treatment | $AUC_{0-72}$ ng*h/ml | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **212.87 ± 123.917** | **35.15 ± 18.913** | **1.25 (0.50-4.50)** |
| **Reference** | **215.56 ± 106.065** | **35.46 ± 16.428** | **1.25 (0.50-3.00)** |
| ***Ratio (90% CI)** | **94.96 (83.24-108.34)** | **94.93 (80.78-111.54)** | **-** |
| **$AUC_{0-72}$** area under the plasma concentration-time curve from time zero to 72 hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum plasma concentration | | | |

**calculated based on ln-transformed data*

For $AUC_{0-72}$ 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 30 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.

Absence of studies with the additional strengths of 15 mg and 30 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 and since the pharmacokinetics of mirtazapine is linear within the recommended dose range.

Based on the submitted bioequivalence study, Mirtazapine Grindeks can be considered bioequivalent with Remeron-S.

**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.

**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 Grindeks.

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 2023-09-01 and proposed the following summary safety concerns:

| | |
|---|---|
| **Important identified risks** | *QT prolongation and/or ventricular arrhythmia (e.g. Torsades de Pointes)* |
| **Important potential risks** | *None* |
| **Missing information** | *None* |

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 2023-09-01 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.

## V. USER CONSULTATION

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. The language used for the purpose of user testing the PL was Latvian.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Mirtazapine Grindeks, is found adequate. There are no objections to approval of Mirtazapine Grindeks, 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.

**List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment**
N/A

**List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC**
N/A

## VII. APPROVAL

The decentralised procedure for Mirtazapine Grindeks, 15 mg, 30 mg, 45 mg, Orodispersible tablet was positively finalised on 2025-07-09.

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# Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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