COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vortioxetine Viatris 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets (vortioxetine hydrobromide)

NL/H/5983/001-004/DC

Date: 26 November 2025

This report reflects the scientific discussion for the approval of Vortioxetine Viatris 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets. The procedure was finalised on 14 March 2025. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Vortioxetine Viatris 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets, from Viatris Limited.

The product is indicated for: the treatment of major depressive episodes in adults.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Brintellix 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets, from H. Lundbeck A/S, which has been registered in the EEA via a centralised procedure (EU/1/13/891) since 18 December 2013.

The concerned member states (CMS) involved in this procedure were Czechia, Denmark, Finland, France, Iceland, Italy (does not apply to the 15 mg strength), Norway, Portugal, Slovakia, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Vortioxetine Viatris 5 mg, 10 mg, 15 mg and 20 mg are film-coated tablets. The four strengths of the film-coated tablets can be distinguished by colour and debossing and are as follows:

Vortioxetine Viatris 5 mg
Pink, oval, film-coated tablets, debossed with '5' on one side and plain on the other side. Each tablet contains vortioxetine hydrobromide equivalent to 5 mg vortioxetine.

Vortioxetine Viatris 10 mg
Yellow, oval, film-coated tablets, debossed with '10' on one side and plain on the other side. Each tablet contains vortioxetine hydrobromide equivalent to 10 mg vortioxetine.

Vortioxetine Viatris 15 mg
Orange, round, film-coated tablets, debossed with '15' on one side and plain on the other side. Each tablet contains vortioxetine hydrobromide equivalent to 15 mg vortioxetine.

Vortioxetine Viatris 20 mg
Red, oval, film-coated tablets, debossed with '20' on one side and plain on the other side. Each tablet contains vortioxetine hydrobromide equivalent to 20 mg vortioxetine.

The excipients are:
Tablet core of all strengths – mannitol, microcrystalline cellulose, sodium starch glycolate (type A), hydroxypropylcellulose and magnesium stearate.
Film-coating of 5 mg – hypromellose, titanium dioxide (E171), macrogol and red iron oxide (E172).
Film-coating of 10 mg – hypromellose, titanium dioxide (E171), macrogol and yellow iron oxide (E172).
Film-coating of 15 mg – hypromellose, titanium dioxide (E171), macrogol, yellow iron oxide (E172) and red iron oxide (E172).
Film-coating of 20 mg – Hypromellose, titanium dioxide (E171), talc, macrogol and red iron oxide (E172).

The four tablet strengths are dose proportional.

The film-coated tablets are packed in either clear, transparent polyvinyl chloride/polyvinylidene chloride/aluminium (PVC/PVDC/Alu) blisters, or clear, transparent polyvinyl chloride/polyethylene/polyvinylidene chloride/aluminium (PVC/PE/PVDC/Alu) blisters.

II.2 Drug Substance

The drug substance is vortioxetine hydrobromide, an established drug substance not described in any Pharmacopoeia. The substance is a white to beige to pale brown powder insoluble in water and has no chiral centers. For this product one polymorphic form is consistently produced.

Two Active Substance Master File (ASMF) procedures are 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/EMA 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.

Manufacturing process
Manufacturer 1 - The manufacturing process consists of four reaction steps followed by drying, physical operations and packing. No class 1 solvents are intentionally added. One possible residual ICH Q3C Class 1 solvent is routinely controlled as per drug substance specification. Adequate specifications have been adopted for starting materials, solvents and reagents. The evaluation of potential genotoxic impurities has been performed in line with ICH M7. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Manufacturer 2 - The manufacturing process consists of five chemical steps including the salt formation and followed by a recrystallisation. No class 1 solvents are intentionally added. The control of possible residual ICH Q3C Class 1 solvents is acceptable. Adequate specifications

have been adopted for starting materials, solvents and reagents. The evaluation of potential genotoxic impurities has been performed in line with ICH M7. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the specification from the ASMF holders. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scaled batches per manufacturer.

Stability of drug substance
Stability data on the active substance have been provided for three consecutive commercial scale batches per manufacturer in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified, and their functions explained. For the formulation development a comparison was made with reference product Brintellix.

Manufacturing process
The manufacturing process is a standard one according to EMA/CHMP/CVMP/QWP/749073/2016, and includes the following steps: wet granulation, tabletting, film-coating, and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of all strengths in accordance with the relevant European guidelines.

Control of excipients
All excipients (including all components but the colourants of the coating agent Opadry) comply with Ph. Eur. requirements. The quality of the colourants red iron oxide and yellow iron oxide comply with regulation 231/2012. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average weight, uniformity of dosage units, identification (of active substance and colourants), water content, assay, dissolution, related substances, N-nitroso vortioxetine content, and microbiological control. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. A nitrosamine risk evaluation has been adequately performed by the MAH and as a result a routine test for N-nitroso vortioxetine has been included in the specification. An elemental impurities risk assessment according to ICH Q3D demonstrated that no further routine control is required.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scale batches of each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided from three commercial scale batches for each strength stored at 25°C/ 60% RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies have been performed in line with ICH Q1B, the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 48 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for the excipient magnesium stearate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vortioxetine Viatris has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH is to undertake comparative dissolution profile testing on the first commercial scale batch of each strength prior to commercialization, in QC medium, in addition to the already provided comparative dissolution profile testing of two commercial scale batches of each strength to fulfil the requirement of three comparative dissolution profile of the first three production batches as per BE guideline.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Vortioxetine Viatris is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Brintellix which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Vortioxetine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Vortioxetine Viatris 5 mg, 10 mg and 20 mg, film-coated tablets (Viatris Limited, Ireland) was compared with the pharmacokinetic profile of the reference product Brintellix 5 mg, 10 mg and 20 mg, film-coated tablets (H. Lundbeck A/S, Denmark).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula for marketing.

Biowaiver

The following general requirements according to the EMA Bioequivalence guideline are met for a waiver for the 15 mg strength:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule).

Dissolution tests complementary to the bioequivalence studies were performed with the same batches as used in the bioequivalence studies. Comparative dissolution profiles at three different media (0.1 N HCl, pH 4.5, 6.8) are submitted. The MAH applied for a biowaiver of strength for the 15 mg tablet, which is dose-proportional to the 20 mg tablet. The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity

factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Vortioxetine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of vortioxetine. Therefore, a food interaction study is not deemed necessary. The bioequivalence studies under fasting conditions are in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Study C1B01103, 5 mg under fasted conditions

Design

An open label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 25-43 years. Each subject received a single dose (5 mg) of one of the two vortioxetine formulations. The tablet was orally administered with 240 mL water after a fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 27 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 6, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 16, 20, 24, 36, 48, 60 and 72 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Out of 42 subjects, 5 subjects were withdrawn from the study (2 subjects due to adverse event of vomiting, 1 subject due to protocol violation and one subject withdrew during period I). 2 subjects had pre-dose concentration greater than 5% of the C_{max}. So per protocol these subjects are excluded from bioequivalence evaluation. 35 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of vortioxetine, 5 mg under fasted conditions.

Treatment N=35	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	92.56 ± 28.24	-	1.93 ± 0.54	11.00 (7.00 – 16.00)
Reference	92.52 ± 30.33	-	1.92 ± 0.55	11.50 (6.50 – 36.00)
***Ratio (90% CI)**	1.00 (0.97 – 1.04)	-	1.01 (0.96 – 1.06)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study C1B02311, 10 mg under fasted conditions

Design

An open label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 25-43 years. Each subject received a single dose (10 mg) of one of the two vortioxetine formulations. The tablet was orally administered with 240 mL water after a fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 29 days.

Blood samples were collected pre-dose and at 1, 3, 5, 6, 7, 8, 9, 9.5 10, 10.25, 10.5, 10.75, 11, 11.25, 11.5, 11.75, 12, 12.5, 13, 14, 16, 18, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject was withdrawn from the study (due to adverse event of vomiting). 31 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of vortioxetine, 10 mg under fasted conditions.

Treatment N=31	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	180.70 ± 46.51	419.18 ± 168.91	3.67 ± 0.98	11.00 (6.00 – 36.02)
Reference	177.52 ± 48.16	431.08 ± 200.95	3.50 ± 0.82	11.00 (7.00 – 24.00)
***Ratio (90% CI)**	1.02 (0.98 – 1.05)	-	1.04 (1.00 – 1.08)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 03578-20-21, 20 mg under fasted conditions

Design

An open label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 21-44 years. Each subject received a single dose (20 mg) of one of the two vortioxetine formulations. The tablet was orally administered with 240 mL water after a fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 25 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 16, 20, 24, 36, 48, 60 and 72 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

17 subjects were withdrawn from the study (2 subjects withdrew due to personal reasons, 11 subjects were withdrawn due to adverse event of vomiting and 4 subjects were withdrawn due to adverse event of loose motions). 25 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of vortioxetine, 20 mg under fasted conditions.

Treatment N=25	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	344.20 ± 75.17	-	8.38 ± 1.69	7.00 (5.00 – 11.50)
Reference	352.86 ± 85.39	-	8.88 ± 2.07	8.50 (5.00 – 10.50)
***Ratio (90% CI)**	0.98 (0.94 – 1.02)	-	0.95 (0.89 – 1.01)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Vortioxetine Viatris is considered bioequivalent with Brintellix.

The results of study 03578-20-21 with the 20 mg formulation can be extrapolated to the 15 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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).

IV.3 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 Vortioxetine Viatris. At the time of approval, the most recent version of the RMP was version 0.2, with date of final sign off 7 August 2024.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	Serotonin Syndrome
Important potential risks	None
Missing information	Off-label paedetric use

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Brintellix. No new clinical studies were conducted. The MAH demonstrated through three bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Brintellix 5 mg, film-coated tablets (EMEA/H/C/002717) for content and to Duloxetine Mylan 30 mg hard gastro-resistant capsules (EMEA/H/C/003981) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vortioxetine Viatris 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Brintellix 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets. Brintellix is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Vortioxetine Viatris with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 March 2025.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-