Post-Authorisation Safety Study Abstract

A non-interventional post-authorisation safety study (PASS) of vortioxetine in Europe

An analysis of European automated healthcare databases

Vortioxetine

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Date of abstract:	02 March 2017

Abstract

Title

A non-interventional post-authorisation safety study (PASS) of vortioxetine in Europe - An analysis of European automated healthcare databases

Rationale and Background

Vortioxetine is a novel antidepressant developed for the treatment of major depressive episodes in adults. Efficacy and safety of vortioxetine have been demonstrated in an extensive clinical programme including more than 5700 patients with major depressive disorder.

Vortioxetine has been granted marketing authorisation in the European Union on 18 December 2013 by the EMA for the treatment of Major Depressive Episodes (MDE) in adults, with a risk management plan (RMP) designed to characterise, monitor and minimise safety concerns associated with vortioxetine. Vortioxetine launch is an opportunity to assess the prescribing practices of this new treatment and to further characterize some important potential risks, as described in the RMP.

Major depressive disorder is frequently treated in primary care. Given the need for unbiased observations to fulfil the study objective and the need to observe large populations to collect enough observations after market entry of vortioxetine, longitudinal automatic healthcare databases are an appropriate tool. Previous studies have also shown that such databases were appropriate to observe use of drugs in specific populations such as children[i,ii,iii,iv,] pregnant women[v] or elderly[vi]. The occurrence of specific events can also be observed as long as the observation is captured as diagnoses or through specific procedures.

Consequently, a post-authorisation safety study (PASS) will be conducted using longitudinal automatic healthcare databases to explore:

- the patterns of use of vortioxetine in some populations or situations considered as important missing information
- the frequency of occurrence of selected important potential risks (suicidal behaviours, convulsions/seizures and severe renal or hepatic events potentially due to precipitation of metabolites in kidney and liver).
- the frequency of events of abuse/dependence for exploratory detection of potential signals, in relation with the important missing information Abuse/Dependence within “Misuse for Illegal Purposes”
- withdrawal due to lack of efficacy in patients aged 75 and over, in relation with the important missing information “Patients Aged 75 and Over”.

The present PASS is part of the RMP as an additional pharmacovigilance activity.

Research Question and Objectives

1) To describe extent of use of vortioxetine in clinical practice by collecting information on the following important missing information:

- Off-label use in terms of indication
- Off-label paediatric use
- Use in pregnant women
- Use in patients aged 75 and over

- Use in patients with a history of mania/hypomania
- Use in patients with the following comorbidities: Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, severe renal or hepatic impairment

2) To further characterise the safety profile of vortioxetine by assessing the frequency of the following events related to important potential risks in patients treated with vortioxetine:

- Suicidal events
- Convulsions/seizures
- Severe renal or hepatic disorders potentially due to precipitation of metabolites in kidney and liver

3) To perform exploratory assessment of the frequency of events of abuse/dependence for detection of potential signals

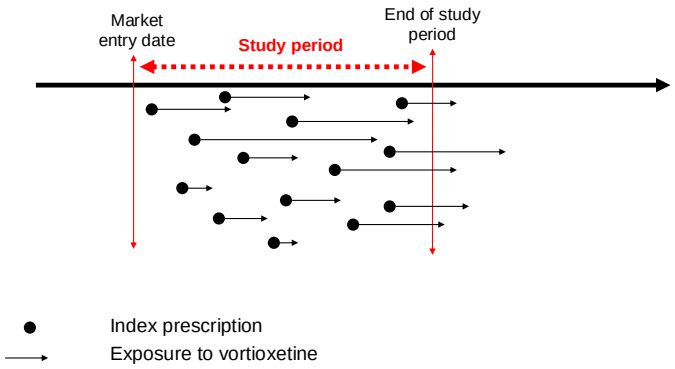
4) To collect information on withdrawal due to lack of efficacy in patients aged 75 and over

Study Design

- *Design*

Historical cohort design using European longitudinal automatic healthcare databases (Figure 1)

Figure 1–Study design



Longitudinal automatic healthcare databases result from the automated collection of prescriptions, diagnoses and other patient characteristics from medical records or insurance claims. Based on a unique patient number, prescription/drug reimbursement claims are recorded in a longitudinal manner, as other variables that may include demographics, indications, hospitalisations and other types of care and procedures. This data collection allows analysing a posteriori the whole patient's prescription and care history within the database.

- *Population and Treatment*

All incident vortioxetine users during the study period (between market entry date and end of study period).

Study period will be the time it takes for the adequate sample size will be reached (see Study Size and Milestones).

For each patient, the date of the first observed prescription of vortioxetine (index prescription) after market entry is called the index date. Exposure starts at the index date and stops either at end of treatment, or at end of study period, or at date of death, or at date of transferred out of the database,

whichever comes first.

Population

- *Study population*

Within the chosen European longitudinal automatic healthcare databases, this PASS will identify a cohort of patients that meet the following criterion for inclusion:

  - Incident prescription of vortioxetine between the date of market entry and the end of the study period

No exclusion criteria will be set.

- *Setting*
  - Databases chosen for this study cover primary and secondary care

Variables

1) To describe extent of use of vortioxetine in clinical practice

- **Off-label use in terms of indication**

- Incident users with no diagnostic codes for depression at index date.

- Diagnostic codes in these patients (such as generalised anxiety disorder, social anxiety disorder, panic disorder, and obsessive-compulsive disorder).

Diagnostic codes will be defined in each database according to the classification in use.

- **Off-label paediatric use**

- Incident users being <18 years old at the time of index prescription.

Age is always present in automatic healthcare databases.

- **Use in pregnant women**

- Incident users with at least one record related to pregnancy during the observed duration of treatment with vortioxetine. *Records related to pregnancy will be further defined in the protocol for each database based on:*

- possibilities for direct identification of pregnancies according to the diagnostic classification in use

- possibilities for identification of pregnancies based on algorithms (published, if any) using additional complementary data including but not limited to prescription, procedures and hospitalisation data (for example, delivery notes).

- **Use in patients aged 75 and over**

- Incident users being ≥ 75 years old during the observed duration of treatment with vortioxetine

Age is always present in automatic healthcare databases.

- **Use in patients with a history of mania/hypomania**

- Incident users with at least one record of diagnosis of bipolar disorder or manic/hypomanic episode any time before the index prescription.

Bipolar disorder and manic/hypomanic episodes will be identified in each database according to the diagnostic classification in use.

- **Use in patients with comorbidities**

- Chronic comorbidities: incident users with at least two records of diagnosis for Alzheimer's disease, Parkinson's disease, multiple sclerosis, or severe chronic renal or hepatic impairment at any time

before the index date.

- Acute comorbidities: incident users with at least one record of diagnosis for acute ischemic or hemorrhagic stroke, or severe acute renal or hepatic impairment in the period up to 1 year before index date.

Comorbidities will be identified in each database according to the diagnostic classification in use.

2) To further characterise the safety profile of vortioxetine by assessing the frequency of events of particular interest

- **Suicidal events**

Events related to suicidal behaviours (suicide attempts, completed suicides) occurring during vortioxetine exposure.

Suicidal events will be further defined in the protocol for each database based on:

- diagnostic codes for suicide attempts

- causes of death for completed suicides (when available).

- **Convulsions/seizures**

Convulsion or seizures events occurring during vortioxetine exposure.

Convulsions/seizures will be identified in each database according to the diagnostic classification in use.

- **Severe renal or hepatic events** potentially **due to precipitation of metabolites in kidney and liver**

Severe renal or hepatic events recorded during vortioxetine exposure.

Severe renal or hepatic events potentially due to precipitation of metabolites in kidney and liver will be defined using the diagnostic classification in use in the databases. Diagnoses codes which will be closest to terms of the following standard MedDRA queries used in clinical trials and reported in the Risk Management Plan will be used: Drug-related hepatic disorders-severe events only; Cholestasis and jaundice of hepatic origin; Acute renal failure.

3) To perform exploratory assessment of the frequency of events of abuse/dependence for detection of potential signals

Events related to abuse/dependence to vortioxetine.

Events related to abuse/dependence will be identified in each database according to the diagnostic classification in use. In the absence of specific codes for abuse/dependence to antidepressants, diagnostic codes of abuse/dependence to drugs will be used, with the exception of codes related to specific drugs such as sedatives, hypnotics or opioids.

4) To collect information on withdrawal due to lack of efficacy in patients aged 75 and over

- Discontinuation of vortioxetine treatment with indication of lack of efficacy in the patients aged 75 and over.

In patients aged 75 and over at index date and treated with therapeutic dose, discontinuation of vortioxetine treatment will be identified within the study period as end of vortioxetine exposure not due to end of study period, or death, or transferred out of the database. In these patients who discontinue vortioxetine as defined above, lack of efficacy will be approached by the presence of a sequence of diagnostic codes indicative of symptoms worsening or of free text from medical records

(when available) evocative of lack of efficacy around the discontinuation date.

- Switch from vortioxetine to another antidepressant treatment in the patients aged 75 and over

In patients aged 75 and over at index date and treated with therapeutic dose, switches from vortioxetine to another antidepressant treatment occurring between 28 and 183 days after the index date will be used as a complementary approach, as treatment change within this time period could indicate discontinuation due to lack of efficacy.

For variables defined according to diagnostic classifications, the list of diagnostic codes will be made available in the study protocol.

Data Sources

- *Countries*

The study will be performed in the Netherlands, in one Nordic country (Norway, Sweden or Finland) and in Spain.

These countries are selected based on the following criteria:

- Presence of adequate and accessible data sources
- Geographic repartition in different European regions
- Launch date (see Timelines) in reasonable timelines

- *Data Sources*

- In Nordic Countries

National prescriptions and patient registers compile and link exhaustive administrative information on all inhabitants (population size is 9.3 million in Sweden, 4.8 million in Norway and 5.3 million in Finland) through the unique social security identifier. Patient characteristics are available, as well as outpatient drug prescriptions (in primary and secondary care), diagnoses (ICD-10 classification), procedures, cause of death. Data is usually made available 1 year after collection[1],[2].

- In the Netherlands

The Pharmo database network links different databases including a general practitioner database (electronic medical records) capturing demographic data, diagnoses (ICPC) and prescriptions. Other outpatient prescriptions can be accessed through the outpatient pharmacy database, and mortality data through the mortality register. The network covers 3 million patients. Data is usually made available 1 year after collection.[3]

- In Spain

The SIDIAP database stores computerised medical records information corresponding to 274 Primary Care Practices in Catalonia, with a total population of 5.8 million patients (80% of the Catalan population). Data recorded includes demographic data, diagnoses (ICD-10 classification), drug dispensation, death and cause of death. Data is usually made available 1 year after collection.[4]

The master protocol will be adapted to the specificities of each database.

[1] http://www.fhi.no/

[2] http://www.socialstyrelsen.se/english/

[3] http://www.pharmo.nl/common

[4] http://www.sidiap.org/index.php?lang=en

To allow describing potential differences in patterns of use across countries if any, but also due to expected technical differences between databases, datasets will not be pooled across countries and analyses will be performed separately in each database.

Study Size

The purpose of the study is descriptive.

Analyses will be performed separately in each database, and the different datasets will not be pooled. The sample size calculation is thus made for each database and relies on the precision estimation with 95% confidence of the prevalence of events of interest, using normal approximation of the binomial distribution.

Based on post-authorisation exposure projections, it is anticipated that the number of patients treated with vortioxetine in the European Union will be 7000 in 2014 and 1.5 million in 2015. Out of a European population of about 500 million, this represents a possible European prevalence of use of 0.3% by the end of 2015. The size of targeted databases is between 5 and 6 million patients. Based on a conservative hypothesis taking into account potential market access delays, it is expected that within one to two years from market entry, at least 2000 exposed patients will be observable in each database.

Thus, assuming a minimum sample size of 2000 patients per database, the expected absolute precision of the estimated events proportions, calculated using a precision estimation with a 95% confidence are presented in Table 1 for each event of interest. Expected events proportions among vortioxetine users in databases were obtained from vortioxetine clinical program studies.

Table 1 - Expected absolute precision of the estimated proportions based on minimal sample size of 2000

	Anticipated events proportions among vortioxetine users*	**Anticipated absolute precision (half 95% confidence interval)**
Suicidal behaviours	0.5%	0.309%
Convulsions	0.1%	0.139%
Hepatic events	0.6%	0.338%
Renal events	0.1%	0.139%

*obtained from vortioxetine clinical studies

Based on the rule-of-three[vii] (according to which a sample size of 3x is necessary to ensure at 95% the detection of at least one event which would have a probability of occurrence at 1/x), a minimum sample size of 2000 patients would allow to detect proportions of users with important missing information of at least 1/666= 0.15%.

Data Analysis

Datasets will not be pooled across countries and analyses will be performed separately in each database. **A master statistical analysis plan will be prepared, and then adapted to the specificities of each database.**

Only descriptive statistics will be used.

All variables, including demographics, will be summarised using descriptive statistics. Summary statistics (mean, standard deviation, median, inter-quartile range, minimum and maximum values) will be presented for continuous variables. Counts and percentages will be presented for categorical and binary variables.

Outcomes will be analysed as follows:

1) To describe extent of use of vortioxetine in clinical practice

- **Off-label use in terms of indication**

- Proportion of incident users without any diagnostic codes for depression near the index date.
- Proportion of each diagnostic code in patients with no diagnostic code related to depression.

- **Off-label paediatric use**

- Proportion of incident users being <18 years old at the time of index prescription.

- **Use in pregnant women**

- Proportion of incident users with at least one record of pregnancy during the observed duration of treatment with vortioxetine

- **Use in patients aged 75 and over**

- Proportion of incident users being ≥ 75 years old during the observed duration of treatment with vortioxetine.

- **Use in patients with a history of mania/hypomania**

- Proportion of incident users presenting with diagnosis of bipolar disorder or manic/hypomanic episode at any point before index date.

- **Use in patients with comorbidities**

- Proportion of incident users presenting with Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, or severe renal or hepatic impairment as described in the "Variables" section.

Descriptive analyses of the characteristics (for example demographics, dose, and medical history) of incident users in the above categories will be included.

2) To further characterise the safety profile of vortioxetine by assessing the frequency of events of particular interest

- **Suicidal events**

- Proportion of incident users presenting events related to suicidal behaviours (suicide attempts, completed suicides) occurring during vortioxetine exposure
- Incidence rate of events related to suicidal behaviours occurring during vortioxetine exposure

- **Convulsions/seizures**

- Proportion of incident users presenting with convulsions/seizures during vortioxetine exposure
- Incidence rate of convulsions/seizures occurring during vortioxetine exposure

- **Severe renal or hepatic disorders** potentially **due to precipitation of metabolites in kidney and liver**

- Proportion of incident users presenting with severe renal or hepatic disorders potentially due to

precipitation of metabolites in kidney and liver as described in the "Variables" section during vortioxetine exposure

- Incidence rate of severe renal or hepatic disorders potentially due to precipitation of metabolites in kidney and liver as described in the "Variables" section occurring during vortioxetine exposure.

3) To perform exploratory assessment of the frequency of events of abuse/dependence for detection of potential signals

- Proportion of incident users presenting with events related to abuse/dependence to vortioxetine.

To take possible confounding factors into account in the analysis, vortioxetine users will be stratified on the presence or absence of concomitant prescriptions of sedatives, hypnotics or opioids and related abuse/dependence events (when available).

- Sensitivity analyses of the occurrence of events related to abuse or dependence to vortioxetine will be performed. In these analyses, the time period will be defined as the treatment exposure period plus one month after treatment discontinuation.

4) To collect information on withdrawal due to lack of efficacy in patients aged 75 and over

- Proportion of incident users aged 75 and over treated at therapeutic dose presenting with discontinuation of vortioxetine treatment with indication of lack of efficacy
- Proportion of incident users aged 75 and over treated at therapeutic dose presenting with a switch from vortioxetine to another antidepressant treatment

Descriptive analyses of the characteristics of incident users presenting these events (for example demographics, dose, and medical history) will be included.

Milestones

Vortioxetine has been launched in the Netherlands in January 2015, in Finland in April 2015 and in Spain in March 2016.

Taking into account the average 12-month time lag, it is proposed to perform assessments of the number of patients prescribed vortioxetine in each database every 6 months starting 24 months after market entry (12 months after market entry plus the minimum of 12 months of time lag) and up until the adequate sample size is reached.

Only when the target sample size (see paragraph **Study Size**) is achieved, will the analysis be performed, as agreed with the EMA.

Time estimtes for each step of the study:
Current date of market entry:

- the Netherlands : January 2015
- Finland: April 2015
- Spain : March 2016.

Registration in the EU PAS register
- May 2017

Date for end of study period: Market entry + **time to reach target sample size**

Data validation and availability: Market entry + **time to reach target sample size** +12 months at the earliest according to database availability date

Statistical reporting (one country): Market entry + **time to reach target sample size** +12 months + 6 months (for statistical analyses of data)

Final study report (all countries): [Market entry + **time to reach target sample size** +12 months + 6 months] of the latest country + 4 months (for reporting of results from all countries)

Timelines are conditional on the date of market entry in each country and on the date when the sample size is achieved.

For information, a worst-case scenario could be a one-year delay in market entry and a period of three years to reach the sample size in the country with the latest market entry. According to this scenario and applying the below timelines, the final study report could be expected in December 2021 at the latest.

References

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