Risk Management Plan

Part VI – Summary of Activities in the Risk Management Plan by Product

Part VI.2. Elements for a Public Summary

Vortioxetine

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Part VI.2 Elements for a Public Summary

Part VI.2.1 Overview of Disease Epidemiology

Major Depressive Disorder (MDD) is a common but serious mental disorder characterised by depressed mood and loss of interest and pleasure in normal activities that interfere with daily life. It is a chronic disease, which often evolves with periods of absence of symptoms followed by recurrence of the disease.

Up to 5 out of 100 people have been depressed in the previous year, and as many as 13 out of 100 are depressed at some point during their life. Depression is twice as common in women as in men and can happen at any age, although it most commonly starts in young adulthood. The reason why some people develop depression is still unknown and seems to depend on a number of factors. It can sometimes be linked to life events (for example, serious illnesses or unemployment).

Depression can lead people to unhealthy behaviours such as smoking and absence of physical exercise. The major danger of depression is suicidal behaviours. The most common diseases accompanying depression are anxiety disorders. In addition patients with depression more commonly have other diseases such as hypertension, diabetes, cancers, epilepsy or migraine. Alcohol and other substance abuse are also commonly present in depressed patients.

Depression is most often treated with psychotherapy and antidepressant medicine.

Part VI.2.2 Summary of Treatment Benefits

There are many drugs available for treating depression, but responses to antidepressants can be variable. Many patients do not get the optimal treatment for their depression and almost half of the patients do not respond to the first antidepressant they try because they do not tolerate the medication or because it does not work. More than 65 out of 100 patients fail to fully recover from their depressive symptoms.

The most commonly prescribed drugs for depression are antidepressants called SSRIs and SNRIs which work primarily by increasing serotonin in the brain. Vortioxetine works in a number of additional and different ways by affecting several systems in the brain activity all

of which are thought to be relevant for depression and involved in cognitive processing such as attention, concentration, and memory.

The clinical programme for vortioxetine consisted of a total of 10 studies (at the time of application for marked authorisation) in adults in which vortioxetine was compared to placebo:

- Nine short-term clinical studies (including a study in elderly patients over 65 years) were performed to show antidepressive effect of vortioxetine.

- A more than one-year study was performed to show that the treatment effect with vortioxetine is maintained over time.

A total of 3394 patients with depression received vortioxetine in these clinical studies.

Vortioxetine demonstrated efficacy in seven out of the nine short-term studies in adults and elderly patients. The effects were measured by traditional and well established methods in depression.

Vortioxetine was also tested in patients whose previous treatment (SSRIs/SNRIs) did not work. This study showed that vortioxetine works and better than another drug on the market, called agomelatine, which also has a different mechanism of action than the SSRI/SNRIs.

All patients with depression, including severely depressed patients, can benefit from the treatment with vortioxetine. Vortioxetine works broadly on all symptoms of depression and has shown positive effects on cognitive function (such as attention, concentration and memory) using specific tests, and on overall functioning in depressed patients. Vortioxetine is effective in depression within the therapeutic dose range of 5-20 mg/day and has shown an increased antidepressive effect with increasing doses.

The antidepressive effect of vortioxetine treatment is maintained with continued treatment.

Patients treated with vortioxetine are two times less likely to have a relapse of their depression compared to placebo.

Part VI.2.3 Unknowns Relating to Treatment Benefits

Vortioxetine has been tested in depressed patients all over the world. It has been tested in patients with different degrees of depression, of different race, in both adults and elderly patients, and in and outside of hospitals. Patients with instable medical illness did not participate in the clinical studies. Vortioxetine worked in short- and in long-term studies and worked independently of the patients' age, sex, race, BMI and history of disease. The antidepressive effect of vortioxetine has not been tested in patients less than 18 years of age, but clinical studies will be performed in the future.

Part VI.2.4 Summary of Safety Concerns

Serotonin syndrome is currently the only *important identified risk* for vortioxetine Table 2. Table 2 provides an overview of the *important potential risks* with vortioxetine and Table 3provides an overview of the *important missing information*.

Table 1 Important Identified Risks

Risk	What is known	Preventability
Serotonin Syndrome	Serotonin syndrome is a drug related syndrome, which is normally associated with treatment with medicines that increase serotonin levels in the brain. If patients are treated with several antidepressants there is an increased risk of serotonin syndrome.	Clinicians should be aware of the symptoms associated with serotonin Syndrome. Dose increases and in particular treatment with medicines that increase serotonin levels should be initiated cautiously.

Table 2 Important Potential Risks

Risk	What is known
Deposit of metabolic product in kidney and liver	Animal studies with high doses of vortioxetine have shown that 2 of the metabolic products of vortioxetine form crystals in the liver and kidney. However, such crystals are unlikely to be formed in humans, as the concentrations of the metabolites in the urine and bile are a lot lower in humans than in animals.
Effects on reproduction	Studies in rats have shown that some pups born to mothers that were treated with vortioxetine during pregnancy did not develop as fast as normally. Some pups were weak at birth and therefore not able to get enough milk at suckling and this resulted in reduced pup survival. As there is a large difference between animals and humans in care for offspring, this is considered a small risk to humans. Vortioxetine did not cause malformations in rats and rabbits. The treatment with vortioxetine did not affect the ability of the animals to mate or get pregnant and did not affect sex organs, sperm quality or early development of the foetus in animals.
Fits (Convulsions/Seizures)	Fits are the result of abnormal electrical changes in the brain. A few episodes of fits have been observed in animals treated with very high doses of vortioxetine. The treatment with other antidepressants that increase serotonin in the brain have been linked with the occurrence of fits in humans, vortioxetine has not been linked to fits in humans.
Suicidal ideations and behaviour	Suicidal ideations and behaviours are common in patients with depression. Studies have suggested that antidepressants may cause these effects in some people, especially young adults and adolescents. In clinical studies, vortioxetine has not been shown to cause these events.
Low sodium level in the blood (Hyponatraemia)	Low sodium levels in the blood are the most common electrolyte disorder especially in the elderly and patients who take medication for high blood pressure or depression. Treatment with other antidepressants that affect serotonin levels has been associated with low sodium levels in particular in the elderly patients. Patients treated with vortioxetine did not have low sodium levels in the blood more often than patients who did not receive treatment.
Bleeding (Haemorrhage)	Some patients have increased bleeding tendencies due to family history of bleeding related diseases. Other patients are at risk when they are treated with medicines that can increase bleeding tendencies like painkillers (such as NSAIDs), blood thinners (such as warfarin) or antidepressants that increase serotonin levels (SSRIs). In clinical studies, patients treated with vortioxetine did not have bleedings more often than patients who did not receive treatment,
Persistent high lung blood pressure in the newborn, PPHN (Persistent pulmonary hypertension in the	The pathway of the baby's blood circulation while still in the mother's womb is different from the one seen after birth, since the baby's lungs are not used in the womb. Normally the blood circulation starts to include the lungs during birth, but in seldom situations this does not happen, because of tightness in the blood vessels of the lungs (a situation known as PPHN).

Risk	What is known
newborn, PPHN)	PPHN has been reported in newborns whose mother's were treated with other antidepressants during their pregnancy. Currently only a few babies were born by mothers treated with vortioxetine during pregnancy; all babies were normal and well after birth.

Table 3 provides an overview of the *important missing information* with vortioxetine.

Table 3 Important Missing Information

Risk	What is known
Use during pregnancy and breast feeding	There is very limited data available on the use of vortioxetine during pregnancy and breast feeding. However a few babies were born by mothers treated with vortioxetine during their pregnancies. All of these babies were well and normal. In animals vortioxetine was found in breast milk. Therefore it is expected that vortioxetine will pass into breast milk in humans as well. Due to the limited information available in humans it is recommended that vortioxetine is not used during pregnancy and breast feeding unless treatment is necessary.
Use in patients with severe kidney or liver disease	One-day studies with vortioxetine in patients with mild and moderate liver disease and with kidney disease, show a similar safety profile compared to patients with normal liver/kidney function. As experience with vortioxetine in patients with severe kidney/ liver disease is limited caution is advised in these patients.
Misuse for illegal purposes	Clinical studies did not indicate that patients would misuse or abuse vortioxetine. It is not expected that patient will misuse vortioxetine for illegal purposes once the drug is on the market, but any misuse will be limited by vortioxetine being available upon prescription only.
Use outside the approved indication	Many antidepressants are approved for a number of psychiatric conditions such as different types of anxiety or obsessions. Vortioxetine is only approved for treatment of depression, and should not be used in other diseases.
Use in children	Treatment of children in general is complicated by the fact that many medicines are not approved for use in their age group. Vortioxetine is only approved for treatment of depression in adults and should not be used in children/adolescents. Studies are ongoing to investigate how vortioxetine works in children and adolescents.
Overdose	During the vortioxetine studies only few patients took doses higher than the maximum recommended dose of 20mg/day. Adverse effects reported in relation to overdoses were similar to those seen in patients treated within the approved dose ranges.
Use in patients aged ≥ 75 years	Overall, effect and safety in elderly patients with depression was similar to what was seen in adults treated with vortioxetine. However elderly patients treated with high doses (20 mg) of vortioxetine experienced more often adverse events like nausea and constipation than patients below the age of 65.

Risk	What is known
	Elderly patients (≥65 years) should start treatment with 5 mg/day of vortioxetine and caution is advised when treating elderly patients with doses higher than 10 mg vortioxetine. Very few patients ≥75 years have been treated with vortioxetine.
Use in depressed patients who also have Alzheimer's disease, Parkinson's disease, multiple sclerosis, and stroke	Patients with Alzheimer's disease, Parkinson's disease, multiple sclerosis, and stroke are more common depressed compared to people without these diseases. However, as these patients were not included in studies with vortioxetine, information about vortioxetine treatment in these patients is limited. Experience from other antidepressants does not indicate that safety or effect should be different compared to other patients with depression.
Use in patients with a history of mania/hypomania (elevated or euphoric mood)	Patients who previously had elevated or euphoric mood were not allowed to participate in studies with vortioxetine therefore these patient should be treated with caution. There is no indication that vortioxetine induced euphoria or elevated mood.

Part VI.2.5 Summary of Additional Risk Minimisation Measures by Safety Concern

No additional risk minimisation measures are warranted for any of the *important identified* and *potential risks* or *important missing information*. Routine risk minimisation in the form of appropriate product labelling and being available only on prescription is considered sufficien-tat this time.

Part VI.2.6 Planned Post Authorisation Development Plan

Table 4 provides an overview of the post authorisation development plan for vortioxetine.

Table 4 List of Studies in the Post Authorisation Development Plan

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
A real life study investigating use of vortioxetine in everyday clinical practice in Europe	1) To describe the use of vortioxetine in real life clinical practice in the patient sub-groups where there is *important missing information* 2) To describe the safety of vortioxetine by assessing if and how often certain important potential risks happen in patients treated with vortioxetine 3) To assess the frequency of symptoms that could indicate abuse/dependence 4) To collect information on patients aged 75 and above who stop their treatment due to not feeling better	*Important potential risks:* o Suicidal ideations and behaviours o Convulsions/ seizures o Severe liver and kidney diseases due to deposits of metabolic products in kidney and liver *Important missing information:* o Use outside of the approved indication o Use in children and adolescents o Use in pregnant women o Use in patients aged ≥ 75 years o Use in patients who previously had mania/hypomania (elevated or euphoric mood) o Use in patients with Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, o Use in patients with severe kidney or liver impairment o Misuse for illegal purposes (Abuse/ Dependence)	Final study protocol (Part VII, Annex VI).	Final Study Report December 2021 at the latest
A controlled study to evaluate the longer-term efficacy of vortioxetine in the treatment of adults with MDD in the USA.	The primary objective is to evaluate the efficacy of vortioxetine (5, 10, and 20 mg) versus placebo during the first 28 weeks of the 32-week double-blind treatment period in the prevention of relapse in subjects with (MDD) who responded to acute treatment with vortioxetine 10 mg.	Overall safety and tolerability measures, including adverse events, laboratory and ECG data.	Study protocol finalised;	Study start: February 2015 Final Report expected 2020
*PRAC- Pharmacovigilance Risk Assessment Committee				

Part VI.2.7 Summary of Changes to the Risk Management Plan over time

This RMP has been updated as per request in EU to update the safety concern Serotonin Syndrome as an identified important risk.