Risk Management Plan

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

Sertindole

Version 4, 4.3.2015

Part VI.2 Elements for a Public Summary

Part VI.2.1 Overview of disease epidemiology

Sertindole is used to treat schizophrenia in patients who have tried and could not tolerate at least one other medication to treat schizophrenia.
Schizophrenia is the most common form of severe mental illness and approximately 24 million people suffer from the illness worldwide. In general, the course of the disorder is long-term, with some short-term episodes of major psychotic symptoms and with longer periods with less marked symptoms, or sometimes recovery, in between. Schizophrenia can make it a challenge to function socially and to manage routine activities of daily living.
The majority of individuals develops schizophrenia between the ages of 15 and 25 years.
At the moment, schizophrenia cannot be cured but the troubling symptoms like hallucinations can be treated effectively with medication. However a significant proportion of patients have a partly or poor response to antipsychotic drugs and then present troubling symptoms.

Part VI.2.2 Summary of treatment benefits

Sertindole is effective in the treatment of schizophrenia.

Four adequate and well-controlled studies established the clinical short-term efficacy of sertindole. These 8-week, placebo-controlled, haloperidol-referenced studies were performed using haloperidol as the comparator because it was the most widely used antipsychotic at the time. The efficacy tool used was a schizophrenia clinical scale, called PANSS which assessed positive symptoms (hallucinations such as hearing voices or thoughts, sometimes seeing things that are not there) and negative symptoms (depression, social withdrawal, lack of motivation, energy or interest in life).

In these 4 studies, both sertindole and haloperidol were more efficacious in the treatment of the positive symptoms of schizophrenia than placebo (sugar pills) was.

One of the most widely used second generation antipsychotics – risperidone – was used as an comparator in a study comparing blindly treatment with sertindole to that of risperidone. Again, sertindole showed efficacy comparable to the comparator.

Long-term efficacy of sertindole has been shown in a 1-year, double-blind, haloperidol-referenced study and further supported by results from two open-label studies of up to 4 years' duration. More than 2700 patients received sertindole during the clinical development.

Part VI.2.3 Unknowns relating to treatment benefits

In a retrospective study, it was shown that proportion of patients who were not hospitalised, or employed, or in a stable relationship was greater during sertindole treatment than during other treatments. Global functioning levels (as measured by the GAF scale) were higher during sertindole treatment than during other antipsychotic treatment.

Part VI.2.4 Summary of safety concerns

Table 5 Important identified risks

Risk	What is known	Preventability
Sudden Cardiac Death	In a large study called SCoP of almost 10 000 patients, the mortality rate of sertindole treated patients was compared to patients treated with another anti-psychotic medication. The overall mortality rate was found to be the same but in the sertindole group, more patients died of heart disease.	Only use sertindole in patients without any contraindications. Regular ECG monitoring. As other drugs also can cause ECG changes or increase the effect of sertindole, it is important that the doctor knows of all medication taken.
Change in the heart's electrical activity on the ECG, resulting in a specific type of arrhythmia **(Torsade de Pointes / QT Prolongation (SMQ))**	Clinical studies have shown that sertindole can change the heart's electrical activity to a greater extent than some other antipsychotics. Therefore, sertindole should only be taken if the patient has tried at least one other anti-psychotic drug. Before starting and during the treatment with sertindole, the doctor should take regular heart traces (ECG) to ensure it stays in the normal range. ECG changes are common during the treatment with sertindole. These changes are often without symptoms but can in some cases increase the risk of more serious heart arrhythmia. Between 1 in every 10 or 100 patients have experienced it.	Only use sertindole in patients without any contraindications. The potential ECG changes can be detected by monitoring and it is important that the patient attend for these check ups at the doctor's. As other drugs also can cause ECG changes or increase the effect of sertindole, it is important that the doctor knows of all medication taken.
Heart disease **(Cardiac Arrhythmia (HLGT))**	During the development of sertindole 16 to 74 in every 1000 patients (in different dose groups) on sertindole compared to 21 in every 1000 patients on sugar pills (placebo) had a side effect related to the heart. Risk factors for heart disease in general include smoking, being overweight, high cholesterol, diabetes and age.	Only use sertindole in patients without any contraindications. Regular ECG monitoring. As other drugs also can cause ECG changes or increase the effect of sertindole, it is important that the doctor knows of all medication taken.
Co-administration of drugs that change in the heart's electrical activity on the ECG, resulting in a specific type of arrhythmia **(Co-administration of drugs that prolong the QT interval)**	Administration of several drugs at the same time can result in interaction with each other. When sertindole is taken, no other drugs should be taken that are able to cause a change in the heart's electrical activity, resulting in a	Do not use sertindole in combination with other drugs that are known to have an effect on the heart's electrical activity. In case you need to take several medications, ask your doctor.

	specific type of arrhythmia.	
Co-administration with drugs that inhibit the activity of certain enzymes (proteins) in the liver that are needed to convert sertindole, and which result in an increased concentration of sertindole **(Co-administration with drugs that inhibit the CYP3A or 2D6)**	Administration of several drugs at the same time can result in interaction with each other. When sertindole is taken, other drugs are able to hinder the breakdown of sertindole, which might result in a higher concentration of sertindole in the blood.	Do not use sertindole in combination with other drugs that are known to interact with these enzymes. In case you need to take several medications, ask your doctor.
Blood clots **(Venous Thromboembolism)**	All anti-psychotic medication, including sertindole, has been linked with blood clots, mainly of the legs (DVT) or the lungs. The frequency of this occurring is not known. Symptoms of blood clots in the legs include swelling, pain and redness in the leg. The blood clot may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. Other risk factors include smoking, age 40+, being overweight, use of oral contraceptives (the pill)/HRT, pregnancy, after surgery, immobility, recent trauma, long-distance travel and cancer. If you notice any of these symptoms seek medical advice immediately.	It is important to reduce the risk factors. It is important to see a doctor immediately if experiencing any symptoms. A blood clot can be treated with blood thinning medication.
Severe reaction to Neuroleptic drugs **(Neuroleptic Malignant Syndrome)**	In placebo-controlled studies, there where no such severe reactions. Rare cases have been reported after sertindole came to the market. It causes fever, muscle stiffness, fast pulse and lower the level of consciousness. Between 1 in every 1000 or 10,000 patients have experienced it.	Treatment should be started promptly and the offending drug(s) should be stopped.
Fits **(convulsion)**	Fits are the result of an abnormal electrical discharge in the brain. Anti-psychotics can lower the threshold for fitting. Fits are uncommon during sertindole treatment. Between 1 in every 100 or 1000 patients have experienced it.	Sertindole should be used with caution in patients with a history of fits. Fits can be treated with anti-convulsive medication.
High blood sugar **(Glucose Metabolism Disorder)**	High blood sugar is uncommon during sertindole treatment. .Between 1 in every 100 or 1000 patients have experienced it.	Monitoring of blood sugar in diabetic patients and those with risk factors for developing diabetes.
Increased level of the hormone	Increased prolactin level is a known effect of anti-psychotic medication	Use of lowest effective dose of sertindole.

prolactin **(Blood Prolactin Increased)**	and has been reported uncommonly with sertindole. Between 1 in every 100 or 1000 patients have experienced it.	Monitor prolactin levels in patients with clinical symptoms

Table 6 Important potential risks

Risk	What is known
Heart failure **(Cardiac Failure)**	Cases of heart failure while on sertindole are being monitored closely but a link to sertindole treatment has not been established. Risk factors include high blood pressure and alcohol. Symptoms include tiredness, shortness of breath and swellings.
Movement disorder **(EPS, including Tardive Dyskinesia)**	Studies in other antipsychotic medications did show that use of this medication is often accompanied with unwanted movements. In studies with sertindole these unwanted movements were observed, but at the same rate as in patients who received sugar pills (placebo). Tardive dyskinesia is a specific form of these kinds of unwanted movements, and is difficult to treat. In the studies with sertindole this specific form was not observed, but as other antipsychotic medication did cause these events, there is a suspicion that sertindole is also able to cause this.
Stroke **(Cerebrovascular Disorder)**	Studies have shown that there is a 3 fold increased risk of strokes in dementia patients using antipsychotics. The mechanism for this increased risk is not known. Strokes, which are a blood clot or a bleeding in the brain, present a problem especially in the older age groups. The consequences of a stroke can be devastating and significantly disable the individual for the rest of his or her life. Sertindole should be used with caution in patients with risk factors for stroke. Sertindole is not approved to be used for behavioural disturbances in dementia. In view of the increased risk factors of stroke in the elderly, sertindole should only be used with care in patients above 65 years of age. Treatment should only be started after a thorough heart examination.
Liver disease **(Hepatic Disorders)**	Medication can cause often a short-lived increase in liver enzymes. Risk factors include drugs, alcohol and infections. Patients with mild and moderate liver disease should receive a lower dose of sertindole. Patients with severe liver disease should not be treated with sertindole. Liver related cases are being monitored closely.
High blood pressure **(Hypertension)**	Cases of high blood pressure reported during sertindole treatment are very few. Risk factors for high blood pressure include age, smoking, overweight, high salt intake, alcohol and lack of exercise. High blood pressure is often without symptoms but can give problems later on if left untreated Blood pressure can be monitored.
Reduced number of white blood cells	This is considered to be a possible risk of all anti-psychotics, a so called class effect. During the development of sertindole 4 in every 1000 patient on

(Leukopenia)	sertindole compared to 3 in every 1000 patients on sugar pills had a side effect related to a reduced number of white blood cells. A low white blood cell count is a decrease in disease-fighting cell and patients experiencing that will be more prone to infections. Monitor patients who are suspected of having a low white blood cell count and treat infections promptly. If drug related, the offending drug should be stopped.

Table 7 Missing information

Risk	What is known
Limited information on use in children and adolescents	Sertindole is not recommended for use in children and adolescents under 18 years of age, due to a lack safety data.
Limited information on use in elderly patients	No difference between young and elderly subjects is observed during studies. However, only limited clinical trial data exist for patients greater than 65 years of age. Therefore, treatment with sertindole should only be started after a thorough examination of your heart, and you should use lower doses than people below the age of 65.
Limited information on use during pregnancy and lactation (breast-feeding)	It was not investigated whether the use of sertindole during pregnancy is safe, therefore sertindole should not be used during pregnancy. Studies in nursing mothers have not been performed, however, it is expected that sertindole will be excreted in breast milk. If treatment with sertindole is considered necessary, consider whether breast-feeding should be continued.

Part VI.2.5 Summary of additional risk minimisation measures by safety concern

The additional risk minimisation measures outlined in table 8 apply to the following risks: Sudden cardiac death, change in the heart's electrical activity on the ECG (Torsade de Pointes / QT Prolongation), heart disease (cardiac arrhythmias) and heart failure (cardiac failure).

Table 8 Safety concerns: Sudden cardiac death, change in the heart's electrical activity on the ECG (Torsade de pointes / QT prolongation), heart disease (cardiac arrhythmias) and heart failure (cardiac failure)

Risk minimisation measures: 1. **Direct Healthcare Professional Communication – DHCPC (Dear Doctor letter)** 2. **Educational material**
Objective and rationale: Additional risk minimisation measures are designed to add to to safe use of sertindole. They are mainly concerned with the explaining and stressing the heart related risks of sertindole and what action should be taken to lower these.
Summary description of main additional risk minimisation measures. Key points: **1** A dear doctor letter (DHCPC) is sent out to all doctors when sertindole becomes available for use. The letter tells the doctor who can use the drug and inform the doctor of risks of sertindole and what he or she must do to lower these. **2** Educational material has been made for both doctors and patients to further help them to understand the advantage and disadvantages of using sertindole.

Part VI.2.6 Planned post authorisation development plan

Table 9 List of studies in the post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final reports**
DUD Denmark	To better understand the usage of sertindole after its return to the market and to relate this usage to potential safety issues.	To get further insight on all listed safety concerns	Completed	March 2010
SCoP (99824) (1) Sertindole versus risperidone safety outcome study: A randomised, partially-blinded, parallel-group, active-controlled, post-marketing study	The overall objective of the study was to compare the safety of sertindole with that of Risperidone under normal conditions of use.	All-cause Mortality (First Primary Endpoint)	Completed	Submitted August 2008

The now completed SCoP Study was a condition of the marketing authorisation.

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

Table 10 Major changes to the Risk Management Plan over time

Version	Date	Safety concerns	Comment
Version 0.1	26/Oct/2005	Identified risks: Cardiovascular events including QT prolongation. Fatal cases and sudden death Potential risks: Class effects of atypical anti-psychotics	First Risk Management Plan Layout of RMP very different from the last and current EU template
Version 0.2	20/Feb/2006	Identified risks: Cardiovascular events including QT prolongation. Fatal cases and sudden death Potential risks: Class effects of atypical anti-psychotics	Layout of RMP very different from the last and current EU template, no change log but same identified risk as in first RMP
Version 0.3	06/May/2008	Identified risks: Cardiovascular events including QT prolongation. Fatal cases and sudden death Potential risks: Hypertension, heart failure, glucose metabolism disorder, cerebrovascular disorders, palpitations, leukopenia, fatal cases, QT Prolongation, asthenia, cardiac disorders, pancreatitis, increased prolactin level and hepatic disorders	Layout of RMP very different from the last and current EU template, no change log or version number. There is no tabular presentation of identified and potential risks and some risks are mentioned both as identified and potential
Version 1	29/Jan/2010	Identified risks: Hypertension, Heart Failure, Glucose Metabolism Disorder Cerebrovascular Disorder Palpitations, Leukopenia Fatal Cases, Electrocardiogram QT Prolongation, Asthenia, Cardiac Disorder, Pancreatitis, Blood	This is the first Risk Management Plan (RMP) where the (*then*) new EU template is used. Content-wise this RMP is similar to the previous one however the layout has been changed considerably. The only new safety concern is the addition of Venous

		Prolactin Increased, Hepatic Disorders Important Potential Risks: Venous Thromboembolism Missing information: Safety and effectiveness in paediatric patients have not been established.	Thromboembolism which is now regarded as a class effect of all anti-psychotics and a warning of this will be incorporated into the EU SPC as of 1st March 2010.
Version 1.1	28/Jun/2010	Identified risks: Hypertension, Heart Failure, Glucose Metabolism Disorder Cerebrovascular Disorder Palpitations, Leukopenia Fatal Cases, Electrocardiogram QT Prolongation, Asthenia, Cardiac Disorder, Pancreatitis, Blood Prolactin Increased, Hepatic Disorders Important Potential Risks: Venous Thromboembolism Missing information: Safety and effectiveness in paediatric patients have not been established.	ESPO clinical study was represented and study report & addendum have been added as a new annex. ESPO study to audit the effectiveness of a safety measure added. (Not approved as suitable) A Danish DUD Study Report added as a new annex to RMP
Version 1.2	21/Jan/2011	Identified risks: Hypertension, Heart Failure, Glucose Metabolism Disorder Cerebrovascular Disorder Palpitations, Leukopenia Fatal Cases, Electrocardiogram QT Prolongation, Asthenia, Cardiac Disorder, Pancreatitis, Blood Prolactin Increased, Hepatic Disorders Important Potential Risks: Venous Thromboembolism Missing information: Safety and effectiveness in paediatric patients have not been established.	A requested Mortality Rate/ Comparative Study to complement the Danish DUD added
Version 2	16/Aug/2011	Identified risks: Hypertension, Heart Failure, Glucose Metabolism Disorder Cerebrovascular Disorder	Updated with the newly proposed study (14290A) on ECG compliance as a planned action. Updated VTE as an

		Palpitations, Leukopenia Fatal Cases, Electrocardiogram QT Prolongation, Asthenia, Cardiac Disorder, Pancreatitis, Blood Prolactin Increased, Hepatic Disorders Venous Thromboembolism Missing information: Safety and effectiveness in paediatric patients have not been established.	identified risk. Annex II Observational Study on ECG Compliance – Protocol Annex III Observational Study on ECG Compliance - Justification document.
Version 3	11/Jan/2013	Neuroleptic malignant syndrome, convulsion and weight gain have been added to the identified risks. Heart failure, cerebrovascular disorder, hepatic disorder, hypertension and leukopenia have been downgraded from identified to potential risks Pancreatitis and asthenia removed as safety concerns.	As a result of the GVP Module V, complete revision of the RMP in the new EU template.
Version 4	11/Jan/2015	Identified Risks: Sudden Cardiac Death, Torsade de Pointes / QT Prolongation (SMQ), Cardiac Arrhythmias (HLGT), Co-administration with drugs that prolong the QT interval, Co-administration of drugs that inhibit CYP3A or 2D6, Venous Thromboembolism, Neuroleptic Malignant Syndrome, Convulsion, Glucose Metabolism Disorder, Blood Prolactin Increased Potential Risks: Heart Failure, EPS including Tardive Dyskinesia, Cerebrovascular Disorder, Hepatic Disorder, Hypertension, Leukopenia Missing information:	Updated with the conclusions from the Assessment Report. Deleted as Important Identified Risk: Fatal cases, Electrocardiogram QT Prolongation, Cardiac Disorders. Updated as an Important Identified Risk: Sudden Cardiac Death, Torsade de Pointed / QT Prolongation (SMQ), Cardiac Arrhythmias (HLGT), Co-administration with drugs that prolong the QT interval, Co-administration of drugs that inhibit CYP3A or 2D6. Updated as Important Potential Risk: EPS including Tardive Dyskinesia.

		Safety in the paediatric population, Safety in elderly patients, Safety in pregnancy and lactation.	