

PUBLIC SUMMARY OF RISK MANAGEMENT PLAN

DATE: 07-10-2015, VERSION 1.1

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Major Depressive Disorder (MDD)

Depression is a medical illness that involves the brain. It is a very common condition that affects around one in every five people. Many factors can cause depression, including the genes (DNA), brain chemistry, and environmental factors like stress. Depression is different from feeling sad or down every now and then. People with depression constantly feel sad, with lack of energy, feel tired, and have difficulty enjoying routine activities almost every day. Not everyone with depression feels sad or down. Other symptoms of depression include: changes in sleeping habits such as sleeping poorly or sleeping more than usual, losing interest in usual activities such as favourite hobbies, time with family members, or evenings out with friends, not eating as much or eating more, whether or not you are hungry, strong feelings of despair, worthlessness, or hopelessness, finding it hard to think or concentrate, feelings of excessive or inappropriate guilt, and thoughts of suicide. Depression is a serious, but treatable, problem that should not be ignored. Many people require some form of treatment by a doctor or other health care professional for their depression. Depression is treated with medicines, talk therapy (talking with a trained professional about thoughts and feelings, sometimes called "psychotherapy" or "counselling"), or a combination of the two. One of these medicines is Venorion which contains an active substance known as venlafaxine.

Generalised Anxiety Disorder (GAD)

Generalised anxiety disorder is a severe, ongoing anxiety condition that interferes with day-to-day activities that occurs in both children and adults. Generalised anxiety disorder is similar in some ways to panic disorder, obsessive-compulsive disorder and other types of anxiety. Living with generalised anxiety disorder can be a long-term challenge. In many cases, it occurs along with other anxiety or mood disorders. In most cases, GAD improves with medications, psychological counselling (psychotherapy), or a combination of the two. Learning how to make lifestyle changes, learning coping skills and using relaxation techniques may be an important part of treatment.

Social Anxiety Disorder (SAD)

Social anxiety disorder, also called social phobia, is a condition in which people have irrational anxiety, fear, self-consciousness and embarrassment around every day social interactions. People with SAD may often realise that their anxiety or fear is out of proportion to the situation. Feelings of shyness or discomfort in certain situations are not necessarily signs of SAD, particularly in children. Comfort levels in social situations vary from individual to individual due to personality traits and life experiences. Some people are naturally reserved and others are more outgoing. What sets SAD apart from every day nervousness is that its symptoms are much more severe and may actually cause patients to avoid normal social situations.

SAD is a chronic mental health condition, but treatment such as psychological counselling, medication and learning coping skills can help patients gain confidence and improve their ability to interact with others. Patients should see their doctor or mental health provider if they have fear and avoid normal social situations because they cause embarrassment, worry or panic.

Panic Disorder

Panic disorder is a condition in which people experience repeated, often unpredictable panic attacks. A panic attack is a sudden episode of intense fear that may trigger severe physical reactions, which occurs when there is no real danger or apparent cause. Panic attacks can be very frightening. When panic attacks occur, patients might think they are losing control, having a heart attack or even dying. Many people have just one or two panic attacks in their life-times, perhaps during stressful situation ends, but don't have persistent attacks. Panic disorder is a chronic mental health condition, but treatment such as psychological counselling, and medication can help patients. Patients should see their doctor or mental health provider if they have unpredictable fear. Panic disorder can be very distressing, but treatment can be very effective.

VI.2.2 Summary of treatment benefits

Venlorion is a prescription medicine used to treat major depressive episodes, generalised anxiety disorder, social anxiety disorder and panic disorder. It belongs to a class of medicines known as SNRIs (which stands for serotonin-norepinephrine reuptake inhibitors). It has not been studied or approved for use in children and adolescents.

The efficacy of venlafaxine for the treatment for major depressive episodes was established in several studies as compared to placebo.

For the treatment of generalised anxiety disorder, venlafaxine was found to be more effective than placebo in four studies.

For social anxiety disorder, efficacy of venlafaxine was established in five studies compared to placebo.

For panic disorder, with or without agoraphobia venlafaxine was found to be more effective than placebo at treating the disorder. In addition, efficacy of venlafaxine was also established in preventing the relapse in adult outpatients.

VI.2.3 Unknowns relating to treatment benefits

There are limited data of use of venlafaxine in patients with severe hepatic impairment.

The efficacy and safety of venlafaxine for the treatment of generalised anxiety disorder, social anxiety disorder and panic disorder with or without agoraphobia in children and adolescents under the age of 18 years have not been established.

There are no adequate data regarding the use of venlafaxine in pregnant women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Symptoms when stopping venlafaxine (discontinuation symptoms or withdrawal syndrome) (Withdrawal syndrome)	Side effects may occur when stopping venlafaxine (discontinuation symptoms), especially when therapy is stopped suddenly. Some of these side effects may include: dizziness, anxiety, nausea, abnormal dreams, headache, tiredness, irritability, sweating, sleeping problems (insomnia), diarrhoea, seizures (convulsions).	Venlafaxine should not be discontinued suddenly. Dose should be reduced gradually. Patients should never stop venlafaxine without first talking to a healthcare provider. If the medication is discontinued, close monitoring for early symptoms of discontinuation is recommended.
Increased blood pressure/Increased heart rate	There have been reports of increase in blood pressure during venlafaxine therapy. Increase in heart rate (feeling of fast heart beat) especially at higher doses can occur during venlafaxine therapy.	All patients should be carefully screened for high blood pressure and pre-existing hypertension (high blood pressure) should be controlled before initiation of treatment. Caution is advised in patients with underlying cardiac disease. Doctor should be informed if the patient develops heart problems such as fast or irregular heart rate, increased blood pressure during venlafaxine therapy. Before starting therapy with venlafaxine the doctor should always be informed if there is any history of high blood pressure, heart problems or abnormal heart rhythm.
Lipid effects (elevated cholesterol, elevated triglycerides and diseases with high levels of lipids in the blood) (Lipid effects (elevated cholesterol, elevated triglycerides and hyperlipidaemias)	Clinically relevant increases in serum cholesterol have been reported with venlafaxine treatment.	Measurement of serum cholesterol levels should be considered during long-term treatment.

Risk	What is known	Preventability
Low sodium levels or (Hyponatraemia)	Venlafaxine can lower the levels of sodium in the blood. Mildly low levels may exist without symptoms. If severe, symptoms can occur including: headache, difficulty concentrating, memory changes, confusion, weakness and unsteadiness on the feet. In very severe cases, symptoms can also include: hallucinations (seeing or hearing things that are not real), fainting, seizures, coma, and even death.	<p>Early symptoms of low sodium levels especially in elderly patients, in patients taking diuretics (water pills), and in dehydrated patients should be closely monitored.</p> <p>Before starting therapy with venlafaxine the doctor should be informed if there is any history of low sodium levels in blood (hyponatraemia).</p>
Fits/Seizures (Convulsion)	Fits/seizures may occur during venlafaxine therapy.	Before starting therapy with venlafaxine the doctor should always be informed if there is any history of fits/seizures.
Serotonin syndrome occurs because the chemical substance known as serotonin is accumulated in the body (Serotonin syndrome)	This is a rare disease that potentially may cause death. It happens when medicines such as venlafaxine are taken with certain other medicines. Patients might have serious changes in how the brain, muscles, heart and blood vessels, and digestive system work. Some symptoms include: restlessness, increase in blood pressure, hallucinations (seeing and hearing things that are not real), diarrhoea, loss of coordination, coma, fast heart beat, nausea, increased body temperature, vomiting, muscle stiffness and/or confusion.	<p>Doctor should be informed if patient is taking, has recently taken or might take any other medicines. Doctor should decide whether patient can take venlafaxine with other medicines.</p> <p>Patient must not start or stop taking any medicines, including those bought without a prescription and herbal remedies, before checking with doctor.</p>

Risk	What is known	Preventability
Suicidality	<p>Venlafaxine is not recommended for use in children and adolescents. Patients under 18 years of age have an increased risk of side effects, such as suicide attempt and suicidal thoughts when they take antidepressants including venlafaxine.</p> <p>Some people may be more at risk of having suicidal thoughts or actions especially if they have (or have a family history of) bipolar illness (also called manic-depressive illness) or if they have had suicidal thoughts or actions in the past.</p>	<p>Early symptoms of suicidality should be monitored. Patients and caregivers should pay close attention to any changes, especially sudden changes, in mood, behaviours, thoughts, or feelings, especially when an antidepressant medicine is started or when the dose is changed. Patients should always keep all scheduled follow-up visits with the healthcare provider.</p> <p>Doctor should write prescriptions of venlafaxine for the smallest quantity of the medicinal product consistent with good patient management.</p> <p>Venlafaxine should normally not be used in children and adolescents under 18 years. The doctor should be informed immediately if any symptoms pertaining to suicide attempt or suicide thoughts arise in this age group.</p>
Abnormal bruising or bleeding such as bruises, nosebleeds, gastrointestinal bleeding, blood spots in the skin to life-threatening haemorrhages (Abnormal bleeding: ecchymoses, haematomas, epistaxis, and petechiae to life-threatening haemorrhages)	Medicinal products like venlafaxine that inhibit serotonin uptake may lead to reduced platelet function. Bleeding events ranging from ecchymoses (bruising), haematomas, epistaxis, and petechiae to gastrointestinal and life-threatening haemorrhages may occur. The risk of haemorrhage may be increased in patients taking venlafaxine. Venlafaxine should be used cautiously in patients predisposed to bleeding, including patients receiving anticoagulants like warfarin and platelet inhibitors.	If patients have unusual bleeding or bruising they need to contact their healthcare provider right away.
Use of venlafaxine with other medicines that can increase the levels of a substance in the body known as serotonin (Interactions with other drugs: Monoamine oxidase inhibitors (MAOIs), serotonergic agents)	Medicines used to treat depression can have a higher effect when administered with other medicines that increase the levels of serotonin in the body.	The patient should always inform the doctor about all medicines he/she is taking before starting treatment with venlafaxine. Patients should not start new medicines without first checking with their healthcare provider.

Risk	What is known	Preventability
Abnormal elevated or irritable mood (Mania/Hypomania)	Mania is a condition in which a person feels and acts very excited, irritable or agitated for a prolonged period. In extreme cases, it may also include dramatic symptoms like hallucinations (perception of something that is not really there), delusion of grandeur, suspiciousness, aggression, or a preoccupation with thoughts and schemes that may lead to self-neglect. In some people, it may show up primarily as catatonic behaviour (immobility and unresponsiveness to the surrounding world). Milder degrees of mania are sometimes called 'hypomania'.	Venlafaxine should be used cautiously in patients with mood disorders or a history or family history of bipolar disorder. Doctor should be informed immediately if the patient develops hyperactivity or euphoria (feeling unusually overexcited) during venlafaxine therapy.
Skin reactions that can progress to produce a disease known as Stevens-Johnson or toxic epidermal necrolysis (Severe Cutaneous Adverse Reactions including Stevens-Johnson Syndrome, Erythema Multiforme, and Toxic Epidermal Necrolysis)	Stevens-Johnson syndrome and toxic epidermal necrolysis are severe diseases characterised by extensive blisters, high fever, sloughing and painful skin. If very severe, they can sometimes be life threatening and may be fatal.	Early symptoms of skin reactions should be monitored; patient should contact a health care provider.
Allergic reaction known as (Anaphylaxis)	Anaphylaxis is an allergic reaction that can range from mild to life-threatening. Patients with mild case may only experience itching, but more severe cases can progress to extreme difficulty in breathing and unconsciousness and can be fatal.	Early symptoms of anaphylaxis should be monitored; patient should contact a health care provider.
Abnormality in the electrocardiogram known as QT prolongation/Torsade de Pointes (TdP)	QT prolongation is an abnormality in the heart's electrical system. Although it doesn't produce symptoms, it sometimes progresses to Torsade de Pointes an abnormal very fast and dangerous heart rhythm. Torsades de pointes may cause persistent palpitations (a sensation of fluttering or pounding in the chest or loss of consciousness) and can be fatal.	Use of venlafaxine in patients with cardiac conduction problems should be avoided. Patients should undergo a prompt medical evaluation for any palpitations (feeling of the heart fluttering or racing). Doctor should be informed if the patient is taking medicines that can affect the heart rhythm such as antiarrhythmics like quinidine (used to treat abnormal heart rhythm), antibiotics like erythromycin or moxifloxacin (used to treat bacterial infections) or antihistamines (used to treat allergy).

Risk	What is known	Preventability
Increased pressure in the eye or (Angle closure glaucoma)	Angle closure glaucoma is a type of glaucoma, which an increase of the pressure in the eye that can result in optic nerve damage and partial or complete loss of vision. Some possible symptoms of angle closure glaucoma include eye pain (sometimes accompanied by nausea and vomiting), sudden onset of vision problems (which may be more noticeable in low light), blurred vision, halos around lights and reddening of the eye.	Before starting treatment with venlafaxine doctor should be informed if patient has any eye problem, such as certain kind of glaucoma (increased pressure in the eye). Also the doctor should be informed if the patient develops eye problems, such as blurred vision, dilated pupils after taking venlafaxine.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Ischaemic cardiac events	Ischemic heart disease (IHD) is a disease where there is not adequate blood supply to the heart. Patients with depression tend to have unhealthy behaviours that increase the risk for the disease. Although there is currently no definitive evidence that antidepressant use causes IHD, patients should be aware of the condition.
Diabetes	Diabetes is a disease characterised by high blood sugar. Mild diabetes may not cause any symptoms, but still can do damage to important body organs. Patients who experience symptoms may notice increased thirst, unusually frequent urination, extreme hunger, unexplained weight loss, fatigue, blurred vision, slow-healing sores, or frequent infections (especially infections of the gums, skin, vagina and bladder). Although, there is currently no definitive evidence that antidepressant use causes diabetes, patients should be aware of the condition.
Aggression including homicidal behaviour	Antidepressants may produce agitation and aggression in depressed patients.

Missing information

Risk	What is known
Limited information on use in elderly patients	No specific dose adjustments of venlafaxine are considered necessary based on patient age alone. However, caution should be exercised in treating the elderly due to the possibility of renal impairment and other changes occurring with aging. The lowest effective dose should always be used, and patients should be carefully monitored when an increase in the dose is required.
Limited information on use in children	The efficacy and safety of venlafaxine for other indications in children and adolescents under the age of 18 have not been established.
Limited information on use in pregnant or lactating women	There are no adequate data from the use of venlafaxine in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Venlafaxine must only be administered to pregnant women if the expected benefits outweigh any possible risk. Women should inform the doctor before starting

Risk	What is known
	<p>the therapy with venlafaxine if they are pregnant. In addition, women should also notify their doctor if they become pregnant, or intend to become pregnant, during therapy.</p> <p>Venlafaxine and its metabolite are excreted in breast milk. There are reports of breast-fed infants who experienced crying, irritability, and abnormal sleep patterns. Symptoms consistent with venlafaxine drug discontinuation have also been reported after stopping breast-feeding. A risk to the suckling child cannot be excluded. Therefore, a decision to continue/discontinue breast-feeding or to continue/discontinue therapy with venlafaxine should be made by the doctor, taking into account the benefit of breast-feeding to the child and the benefit of venlafaxine therapy to the woman.</p>
Limited information on use in patients with severe impairment of liver function	There are limited data in patients with severe hepatic impairment.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures. The Summary of Product Characteristics and the Package leaflet for Venorion can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable.