## 13.2 Part VI.2 Elements for a Public Summary

### 13.2.1 Part VI.2.1 Overview of disease epidemiology

**Major depressive episodes**

Depression is a common mental disorder. Globally, an estimated 350 million people of all ages suffer from depression. More women are affected by depression than men. Long-lasting depression with moderate or severe intensity may become a serious health condition. At its worst, depression can lead to suicide [WHO, 2016].

Depressive disorders often start at a young age; they reduce people's functioning and often are recurring making depression the leading cause of disability worldwide. Lifetime prevalence (proportion of a population that at some point in their life have experienced the condition) of depression is approximately 3% in Japan, 16.9% in the United States, and between 8 to 12% in most other countries [Marcus M, 2012].

In Europe each year, 25% of the population suffers from depression or anxiety, up to 50% of chronic sick leaves are due to depression/anxiety and about 50% of major depressions (MD) are untreated [WHO Europe, 2016].

**Generalized anxiety disorder (GAD)**

GAD is characterized by persistent, excessive, and unrealistic worry about everyday things. GAD affects 6.8 million adults, or 3.1% of the U.S. population, in any given year. Women are twice as likely to be affected. The disorder progresses slowly and can begin across the life cycle, with risk being highest between childhood and middle age. Biological factors, family background, and life experiences, particularly stressful ones, play a role in causing GAD [ADAA, 2015].

Surveys in Europe suggest that lifetime prevalence of GAD is 4.3–5.9%. MD is present in three out of five cases of GAD and a similar proportion has other anxiety disorders. Only two out of five patients seek treatment for GAD and for these patients the rates of full or partial remission (disappearance of the signs and symptoms) in the long term (5 years or more) are fairly disappointing at 38–41% [Tyrer P, 2006].

**Social anxiety disorder (SAD)**

SAD is the extreme fear of being carefully examined and judged by others in social or performance situations. Symptoms may be so extreme that they disrupt daily life. People with this disorder, also called social phobia, may have few or no social or romantic relationships, making them feel powerless, alone, or ashamed. About 15 million American adults have SAD. Typical age of onset is 13 years. 36 percent of people with SAD report symptoms for 10 or more years before seeking help. SAD usually begins in childhood or adolescence, and children are prone to clinging behavior, tantrums, and even mutism (inability to speak and communicate) [ADAA, 2016].

Surveys conducted across Europe indicate that lifetime prevalence of SAD in the general population is 7%. The disorder in adulthood rarely presents in its 'pure' form and 70-80% of

patients have at least one other psychiatric disorder, most commonly depression [Lecrubier Y, 2000].

**Panic disorder, with or without agoraphobia**

Panic disorder is a common mental disorder with 4.7% lifetime occurence in general population. Studies have shown that females are affected more and common age of onset is late adolescence or early adulthood. Childhood panic is more common in the offspring of parents with panic disorder [Roy-Byrne PP, 2006].

About six million American adults experience panic disorder every year. Some people stop going into situations or places in which they have previously had a panic attack fearing that it might happen again, these people have agoraphobia (fear of open spaces). About one in three people with panic disorder develops agoraphobia. Panic disorder occurs with other mental and physical disorders, including other anxiety disorders, depression, irritable bowel syndrome, asthma, or substance abuse [ADAA Panic, 2016].

It is often disabling, and is associated with functional disorder and reduced quality of life. It is costly for individuals and society [Roy-Byrne PP, 2006].

### 13.2.2 Part VI.2.2 Summary of treatment benefits

Selective Serotonin Reuptake Inhibitors (SSRIs) (class of drugs used in the treatment of major depressive and anxiety disorders) are considered as first-line treatment in major depressive disorder (MDD). According to a combined analysis of 26 studies comparing venlafaxine with an SSRI, there is evidence that venlafaxine is more effective than several antidepressants (medicines used in the treatment of major depressive and anxiety disorders) in the treatment of MDD [de Silva VA, 2012].

A large, multisite, study evaluating the long-term safety and efficacy of venlafaxine Extended Release (ER) (pill which releases medicine slowly into bloodstream) in patients of depression receiving a range of doses from 75 to 300 mg/day including 1-year maintenance phase with venlafaxine known as Prevention of Recurrent Episodes of Depression with Venlafaxine ER for Two Years (PREVENT) was conducted. An analysis of data from the PREVENT study was conducted to estimate the probability of remaining well at a dose of venlafaxine ER ≤225 mg/day over 2.5 years of follow-up. The results of analysis confirmed that chances of remaining well was greater for patients receiving venlafaxine compared with those receiving placebo (dummy medication) [Kornstein SG, 2008].

A study conducted in 541 patients, 18-86 years old, over 24-week showed that Venlafaxine ER is an effective and safe treatment for GAD [Allgulander C, 2001].

In a study with total of 440 patients out of which 146 patients received venlafaxine ER, 147 received paroxetine (drug used to treat anxiety and depressive disorders) and 147 received placebo Venlafaxine ER was shown to be effective in the short-term treatment of generalized SAD, with efficacy and tolerability comparable to paroxetine [Liebowitz MR, 2005].

Several studies have demonstrated short-term and long-term efficacy of venlafaxine in panic disorder. Venlafaxine can be used confidently in patients with panic disorder and its depression and anxiety comorbidities [Katzman MA, 2007].

### 13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

The efficacy of venlafaxine for other indications in children and adolescents under the age of 18 years has not been established.

The efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, has not been established.

## 13.2.4 Part VI.2.4 Summary of safety concerns

**Table 13-2 Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Set of symptoms occurring due to discontinuation or dosage reduction of the drug<br>(Withdrawal syndrome) | Side effects i.e. withdrawal reactions are known to occur when people stop using this medicine, especially when it is stopped suddenly or the dose is reduced too quickly. Some patients may experience symptoms such as tiredness, dizziness, light-headedness, headache, sleeplessness, nightmares, dry mouth, loss of appetite, nausea, diarrhea, nervousness, agitation, confusion, ringing in the ears, tingling or rarely electric shock sensations, weakness, sweating, fit episodes, or flu-like symptoms. | Patients should not stop taking venlafaxine treatment or reduce the dose without the advice of their doctor even if they feel better. If the doctor thinks that patients no longer need venlafaxine, he/she may ask them to reduce the dose slowly before stopping treatment altogether. The doctor advises on how the treatment should be discontinued slowly.<br><br>If patients experience any of mentioned or other symptoms that are troublesome, they should ask their doctor for further advice. |
| Increased blood pressure/Increased heart rate | Increase in blood pressure is a common side effect of venlafaxine.<br><br>Fast heartbeat is an uncommon side effect of venlafaxine.<br><br>Metoprolol (a beta blocker to treat high blood pressure and heart problems) may interact with venlafaxine.<br><br>The symptoms of a possible overdose may include a rapid heartbeat | If patients have history of heart problems such as fast or irregular heart rate or high blood pressure they should talk to their doctor before taking venlafaxine.<br><br>Patients should inform their doctor if they experience heart problems, such as fast or irregular heart rate, increased blood pressure with use of venlafaxine.<br><br>Metoprolol should be used with caution and doctor or pharmacist should be informed if patients are using this medicine along with venlafaxine.<br><br>Patients should contact their doctor or pharmacist immediately if they take more of venlafaxine than the amount prescribed by the doctor. |

| Risk | What is known | Preventability |
|---|---|---|
| Lipid effects<br>(elevated cholesterol, elevated triglycerides and hyperlipidemias) | Increased cholesterol is a common (may affect up to 1 in 10 people) side effect of venlafaxine. | Venlafaxine sometimes causes unwanted effects that patients might not be aware of, such as slight changes in blood levels of cholesterol. Therefore, doctor should do blood tests occasionally, particularly if patients have been taking venlafaxine depot for a long time. |
| Decreased sodium levels in the blood<br>(Hyponatremia) | Excessive water intake (known as Syndrome of Inappropriate Antidiuretic Hormone (SIADH)) and decrease in blood sodium levels are side effects which occur at a rare (may affect up to 1 in 1,000 people) with the use of venlafaxine. | Patients should inform their doctor before taking venlafaxine if they a history of low sodium levels in their blood (hyponatremia).<br><br>Venlafaxine sometimes causes unwanted effects that patients might not be aware of, such as slight changes in blood levels of sodium. Therefore, doctor should do blood tests occasionally, particularly if patients have been taking venlafaxine depot for a long time. |
| A medical condition in which person's body shakes rapidly and uncontrollably<br>(Convulsion) | Seizures or fits are rare (may affect up to 1 in 1,000 people) side effects of venlafaxine.<br><br>The symptoms of a possible overdose may include seizures or fits. | Patients should inform their doctor before taking venlafaxine if they had a history of fits (seizures).<br><br>Patients should contact their doctor or pharmacist immediately if they take more of venlafaxine than the amount prescribed by the doctor.<br><br>Patients should inform their doctor if they experience nerve problems, such as seizures or fits. |

| Risk | What is known | Preventability |
|---|---|---|
| A potentially life-threatening condition due to drug interaction<br>(Serotonin syndrome) | A potentially life-threatening condition or Neuroleptic Malignant Syndrome (NMS) (life-threatening, nerve disorder most often caused by an adverse reaction to psychiatric drugs) - like reactions, may occur with venlafaxine treatment, particularly when taken with below medicines.<br>Examples of these medicines include:<br>• Triptans (used for migraine)<br>• Other medicines to treat depression, for instance SNRIs, SSRIs, tricyclics, or medicines containing lithium<br>• Medicines containing linezolid, an antibiotic (used to treat infections)<br>• Medicines containing moclobemide, a MAOI (used to treat depression)<br>• Medicines containing sibutramine (used for weight loss)<br>• Medicines containing tramadol, fentanyl, tapentadol, pethidine or pentazocine (used to treat severe pain).<br>• Medicines containing dextromethorphan (used to treat coughing)<br>• Medicines containing methadone (used to treat opioid drug addiction or severe pain)<br>• Medicines containing methylene blue (used to treat high levels of methemoglobin in the blood)<br>• Products containing St. John's Wort (also called Hypericum perforatum, a natural or herbal remedy used to treat mild depression)<br>• Products containing tryptophan (used for problems such as sleep and depression) | Patients should not take venlafaxine if they are also taking, or have taken within the last 14 days, any medicines known as irreversible Monoamine Oxidase Inhibitors (MAOIs), used to treat depression or Parkinson's disease (a slowly progressive nervous disease affecting movements in body). Also, they should wait at least 7 days after stopping venlafaxine before they take any MAOI.<br><br>Patients should inform their doctor before taking venlafaxine if they use other medicines that taken together with venlafaxine could increase the risk of developing serotonin syndrome.<br><br>Patients should inform their doctor immediately, or go to the casualty department at the nearest hospital if they think serotonin syndrome is happening to them. |

| Risk | What is known | Preventability |
|---|---|---|
| | • Antipsychotics (used to treat a disease with symptoms such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, unclear reasoning and becoming withdrawn).<br><br>Signs and symptoms of serotonin syndrome may include a combination of the following: restlessness, hallucinations, loss of coordination, fast heartbeat, increased body temperature, fast changes in blood pressure, overactive reflexes, diarrhea, coma, nausea and vomiting, and occur at a rare frequency (may affect up to 1 in 1,000 people).<br><br>In its most severe form, serotonin syndrome can resemble Neuroleptic Malignant Syndrome (NMS). Signs and symptoms of NMS may include a combination of fever, fast heartbeat, sweating, severe muscle stiffness, confusion, increased muscles enzymes (determined by a blood test). | |
| Thoughts of harming or killing oneself<br>(Suicidality) | Some people who are depressed may think of harming or killing themselves. These thoughts may be increased when patients first start taking antidepressants, since these medicines all take time to work, usually about two weeks, but sometimes longer.<br><br>Patients who have previously had thoughts about killing or harming themselves and young adults are more likely to have these thoughts.<br><br>Patients under 18 have an increased risk of side effects, such as suicide attempt or suicidal thoughts when they take this class of medicines. | Patients should see their doctor or go to a hospital straight away if they have thoughts of killing or harming themselves.<br><br>Patients might find it helpful to tell a relative or close friend that they are depressed or have an anxiety disorder, and should ask them to read the patient information leaflet. Patients should also ask their relatives or friends to tell them if they think depression or anxiety symptoms are getting worse, or if they are worried about changes in patients' behavior.<br><br>Patients should inform their doctor if suicidal thoughts develop or worsen when patients under 18 are taking venlafaxine. |

| Risk | What is known | Preventability |
|---|---|---|
| | Cases of suicidal ideation and suicidal behaviors have been reported during venlafaxine therapy or early after treatment discontinuation at an unknown frequency. | |
| Abnormal bleeding of skin and mucous membranes (Abnormal bleeding: ecchymoses, hematomas, epistaxis and petechie to life-threatening hemorrhages) | Vomiting blood, black tarry stools (feces) or blood in stools, which can be a sign of internal bleeding are uncommon (may affect up to 1 in 100 people) side effects of venlafaxine.<br><br>Reduced number of platelets in blood, leading to an increased risk of bruising or bleeding, unexpected bleeding, e.g. bleeding gums, blood in the urine or in vomit, or the appearance of unexpected bruises or broken blood vessels (broken veins) may occur at a very rare frequency (may affect up to 1 in 10,000 people) with the use of venlafaxine. | Patients should inform their doctor before taking venlafaxine if they have a tendency to develop bruises or a tendency to bleed easily (history of bleeding disorders), or if they are taking other medicines that may increase the risk of bleeding e.g., warfarin (used to prevent blood clots).<br><br>Patients should inform their doctor if they experience prolonged bleeding (it takes slightly longer than usual for bleeding to stop if patients cut or injure themselves) with venlafaxine use. |
| Interaction with psychiatric drugs that act by blocking the chemical's action completely and are used for the treatment of depression (Interactions with other drugs: MAOIs, Serotonergic agents) | Taking an irreversible MAOI together with venlafaxine, can cause serious or even life-threatening side effects called serotonin syndrome. | Patients should not take venlafaxine if they are also taking, or have taken within the last 14 days, any medicines known as irreversible MAOIs, used to treat depression or Parkinson's disease. Also, they should wait at least 7 days after stopping venlafaxine before they take any MAOI. |
| Feeling elated or over-excited, which causes unusual behavior, hypomania generally less severe than full mania (Mania/Hypomania) | Over activity, racing thoughts and decreased need for sleep (mania) are uncommon (may affect up to 1 in 100 people) side effects of venlafaxine. | Patients should inform their doctor before taking venlafaxine if they have a history of, or if someone in their family has had, mania or bipolar disorder (feeling over-excited or euphoric). |
| Severe cutaneous a reactions (SCAR) including SJS, Erythema multiforme (EM) and TEN | Severe skin rash, itching which may lead to severe blistering (a small bubble on the skin filled with serum (clear liquid that can be separated from clotted blood)) and peeling of the skin, or hives (elevated patches of red or pale skin that often itch) may occur at a rare frequency (may affect up to 1 in 1,000 people) with the use of venlafaxine. | Patients should not take venlafaxine if they are allergic to venlafaxine or any of the other ingredients of this medicine.<br><br>If severe rash, itching, or hives happen patients should inform their doctor immediately or go to the casualty department at the nearest hospital. |

| Risk | What is known | Preventability |
|---|---|---|
| Allergic reaction (Anaphylaxis) | Shortness of breath, vomiting, mild rash and itching may occur at a common frequency with the use of venlafaxine.<br><br>Swelling of the face, mouth, tongue, throat, hands, or feet, and/or a raised itchy rash (hives), trouble swallowing or breathing are uncommon (may affect up to 1 in 100 people) side effects of venlafaxine.<br><br>Severe skin rash, itching which may lead to severe blistering and peeling of the skin, or hives may occur at a rare frequency (may affect up to 1 in 1,000 people) with the use of venlafaxine. | Patients should not take venlafaxine if they are allergic to venlafaxine or any of the other ingredients of this medicine.<br><br>If severe rash, itching, or hives (elevated patches of red or pale skin that often itch) happen patients should inform their doctor immediately or go to the casualty department at the nearest hospital. |
| Abnormal ECG pattern/abnormal heart rhythm including uncommon and unique type of rapid fast beat (Torsade de Pointes [TdP]) caused by the lower chambers of the heart, the ventricles (QT prolongation/ TdP | Fast heartbeat, palpitations (rapid, strong and irregular heartbeat) may occur at a common frequency (may affect up to 1 in 10 people) with the use of venlafaxine.<br><br>The symptoms of a possible overdose may include a rapid heartbeat. | If patients have history of heart problems such as fast or irregular heart rate or have an abnormal heart rhythm they should talk to their doctor before taking venlafaxine.<br><br>Patients should talk to their doctor if they are taking below medicines that can affect their heart rhythm.<br>Examples of these medicines include:<br>• Antiarrhythmic such as quinidine, amiodarone, sotalol or dofetilide (used to treat abnormal heart rhythm)<br>• Antipsychotics such as thioridazine<br>• Antibiotics such as erythromycin or moxifloxacin (used to treat bacterial infections)<br>• Antihistamines (used to treat allergy)<br><br>Patients should inform their doctor if they experience heart problems, such as fast or irregular heart rate, with use of venlafaxine. |

| Risk | What is known | Preventability |
|---|---|---|
| An ocular/eye condition caused by a rapid or sudden increase in intraocular pressure , the pressure inside the eye that might result in loos of vision if left untreated<br>(Angle closure glaucoma) | Visual disturbance including blurred vision; dilated pupils (hole located in the center of the eye); inability of the eye to automatically change focus from distant to near objects, are common (may affect up to 1 in 10 people) side effects which may occur with the use of venlafaxine. | Patients should inform their doctor before taking venlafaxine if they have eye problems, such as certain kinds of glaucoma (increased pressure in the eye). |

**Table 13-3 Important potential risks**

| Risk | What is known |
|---|---|
| Events due to decreased oxygen in the heart<br>(Ischemic cardiac events) | Before taking venlafaxine, the doctor should be informed if the patient has a history of heart problems.<br><br>Venlafaxine has not been evaluated in patients with a recent history of heart attack or unstable heart disease. Therefore, it should be used with caution in these patients.<br><br>Fast heartbeat, palpitations, shortness of breath and flushing (skin or face becomes red and hot) are common (may affect up to 1 in 10 people) side effects of venlafaxine drug. |
| Disease with increased blood sugar levels<br>(Diabetes) | Blood glucose levels may be altered due to venlafaxine. Therefore, the dosage of medicines used to control the blood sugar levels may need to be adjusted. |
| Range of behaviors that can result in both physical and psychological harm to oneself or to others<br>(Aggression including homicidal behavior) | Currently no adequate data are available about the association of misuse of venlafaxine. |

**Table 13-4 Missing information**

| Risk | What is known |
|---|---|
| Use in elderly patients | Caution should be exercised in treating the elderly (e.g., due to the possibility of kidney abnormal functioning, the potential (possibility) for changes in neurotransmitter (a chemical produced by brain cells) sensitivity and affinity (a liking for someone or something) occurring with aging).<br><br>Elderly patients taking diuretics may be at greater risk for hyponatremia. |
| Use in children<br>(Use in pediatric patients) | The efficacy and safety of venlafaxine for other indications in children and adolescents under the age of 18 have not been established. |

| Risk | What is known |
|---|---|
| | Venlafaxine should normally not be used for children and adolescents under 18 years. Patients under 18 have an increased risk of side effects, such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behavior and anger) when they take this class of medicines.<br><br>Despite this, doctor may prescribe this medicine for patients under 18 because he/she decides that this is in their best interests. If the doctor has prescribed this medicine for a patient under 18, and the patient might want to discuss this, then please go back to the doctor and discuss.<br><br>Patient should inform the doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking venlafaxine.<br><br>The long-term safety effects concerning growth, maturation and cognitive and behavioral development of this medicine in this age group has not yet been demonstrated. |
| Use in pregnancy and lactation | Doctor should be informed if the patient is pregnant or trying to become pregnant. Patient should use venlafaxine only after discussing the potential benefits and the potential risks to the unborn child with the doctor.<br><br>Pregnant women should inform the midwife/physician if they are on venlafaxine treatment. When taken during pregnancy, similar drugs (SSRIs) may increase the risk of a serious condition in babies, called PPHN, making the baby breathe faster and appear bluish and not feeding properly. These symptoms usually begin during the first 24 hours after the baby is born.<br><br>Pregnant women should inform the physician immediately if signs of PPHN are observed with baby.<br><br>Venlafaxine passes into breast milk. There is a risk of an effect on the baby. Therefore, patient should discuss the matter with the doctor, and he/she will decide whether the patient should stop breast-feeding or stop the therapy with this medicine. |
| Use in severe liver problems<br>(Use in severe hepatic impairment) | Limited information is available about the use of venlafaxine in patients with severe liver problems. Precaution should be taken and 50% dose reduction should be considered. The potential benefit should be weighed against the risk in the treatment of patients with severe liver dysfunction.<br><br>Patients should inform the doctor if they have liver problems, since their dose of this medicine may need to be adjusted accordingly. |

### 13.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals (HCPs) with details on how to use the medicine, the risks and recommendations for minimizing 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 minimization measures.

This medicine has no additional risk minimization measures.

### 13.2.6 Part VI.2.6 Planned post authorization development plan

None

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

N/A (first submission)