VI.2 Elements for a Public Summary

V.2.1 Overview of disease epidemiology

Major depression is manifested by a combination of symptoms that interfere with the ability to work, study, sleep, eat, and enjoy once pleasurable activities. Disabling episodes of depression may occur only once, but more commonly reoccur several times in a lifetime. Treatment choice will depend on the outcome of the evaluation. People with moderate to severe depression most often benefit from antidepressants. In any given 1-year period, 9.5% of the population, suffer from a depressive illness [(1)] ,with the World Health Organisation (WHO) estimating that depression affects 350 million people with the burden 50% higher for females than males.

Generalised anxiety disorder (GAD) is characterised by worries based on extant dangers whose likelihood is overestimated and whose negative consequences are exaggerated. GAD patients may suffer from physical symptoms such as fatigue, headaches, muscle tension, muscle aches, difficulty swallowing, trembling, twitching, irritability, sweating, hot flashes and sleep disorders GAD is experienced by 4.3% to 5.9% of people during their lifetime and 0.2% to 4.3% population experience GAD each year. [(42)]

Social phobia, also called **social anxiety disorder**, involves overwhelming anxiety and excessive self-consciousness in everyday social situations. Physical symptoms often accompany the intense anxiety of social phobia and include blushing, profuse sweating, trembling, nausea, and difficulty talking. Social phobia affects about 2.6 percent of the population [(43)] and women and men are equally likely to develop social phobia [(44).]

Panic disorders experience brief attacks of intense terror and apprehension, often marked by trembling, shaking, confusion, dizziness, nausea, and/or difficulty breathing. The frequency of panic disorder is estimated by WHO [(45)] to be similar across the globe, with age-standardised prevalence (proportion of the population experiencing the disease) ranging from 300-350 per 100,000 for men and nearly double in women, estimated at around 600-650 per 100,000 [(46)]. **Agoraphobia** is also strongly linked with panic disorder and is often precipitated by the fear of having a panic attack although agoraphobia is a specific anxiety about being in a place or situation where escape is difficult or embarrassing.

VI.2.2 Summary of treatment benefits

The summary of treatment benefits is summarised from information available in the SmPC of the reference product. The efficacy of venlafaxine prolonged-release as a treatment for **major depressive episodes** was established in several studies, one short-term study (8-12 weeks), another for up to 26 weeks and a further 12 month study, all placebo controlled and randomised and using standard therapeutic doses of 75 to 225 mg/day. The efficacy of venlafaxine as a treatment for **GAD** was established in two 8-week, placebo-controlled, fixed-dose studies (75 to 225 mg/day), one 6-month, placebo-controlled, fixed-dose study (75 to 225 mg/day), and one 6-month, placebo-controlled, flexible-dose study (37.5, 75, and 150 mg/day) in adult outpatients, although the low dose was not consistently effective. The efficacy of venlafaxine as a treatment for **social anxiety disorder** was established in four double-blind, parallel-group, 12-week, multi-centre, placebo-controlled, flexible-dose studies and one double-blind, parallel-group, 6-month, placebo-controlled, fixed/flexible-dose study in adult outpatients. Patients received doses in a range of 75 to 225 mg/day. There was no evidence for any greater effectiveness of the 150 to 225 mg/day group compared to the 75 mg/day group in the 6-month study. The efficacy of venlafaxine as a treatment for **panic disorder** was established in two double-blind, 12-week, multi-centre, placebo-controlled studies in adult outpatients with panic disorder, with or without agoraphobia. The initial dose in panic disorder studies was 37.5 mg/day for 7 days. Patients then

received fixed doses of 75 or 150 mg/day in one study and 75 or 225 mg/day in the other study. Efficacy was also established in one long-term double-blind, placebo-controlled, parallel-group study of the long-term safety, efficacy, and prevention of relapse in adult outpatients who responded to open-label treatment.

VI.2.3 Unknowns relating to treatment benefits

There are no significant unknowns regarding the efficacy studies of venlafaxine in the target population.

VI.2.4 Summary of safety concerns

Table 50. Important identified risks

Risk	**What is known**	**Preventability**
Symptoms when stopping venlafaxine (Withdrawal syndrome)	Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia - a sensation of tingling, tickling, pricking, or burning of a person's skin with no apparent physical cause), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, vertigo, headache and flu syndrome are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting; however, in some patients, they may be severe and/or prolonged. It is therefore advised that when venlafaxine treatment is no longer required, gradual discontinuation by dose tapering should be carried out.	YES, the SmPC and PL clearly indicate that withdrawal symptoms are an important risk when discontinuing therapy. The symptoms are clearly defined to help patients and HCPs identify when there is a problem and appropriate information is also included to decrease the likelihood of experiencing these complications.

Suicidality	Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide related events). This risk persists until significant remission occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. In addition, studies have shown an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old (see separate safety concern for more details).	YES, the SmPC and PL clearly indicate the risks of suicide-related behaviours in the target population, especially during the early phase of treatment, and suggest ways, such as increased monitoring, to decrease the likelihood of patients taking action during treatment until remission occurs. In addition, use of venlafaxine prolonged-release tablets is not recommended in the paediatric population. However, development of suicide behaviour in some patients will be impossible to predict or prevent, especially during early phases of treatment, but the SmPC and PL indicate measures to take to identify and minimise risks.

Risk	**What is known**	**Preventability**
Serotonin syndrome occurs because the chemical substance known as serotonin is accumulated in the body. This can occur with associated use of other medications (used mainly in neurology and psychiatry)	The development of a potentially life-threatening serotonin syndrome can occur when venlafaxine is used concomitantly with several classes of drugs in addition to drugs called monoamine oxidase inhibitors (MAOIs) and other concomitant drug such as serotonergic drugs, hallucinogens, dextromethorphan (DXM)/dextrorphan (DXO), tramadol, tapentadol, meperidine/pethidine and triptans. Serotonin syndrome symptoms include agitation, hallucinations, coma, tachycardia (fast heart rate), blood pressure changes, hyperthermia, hyperreflexia (overactive reflexes), incoordination, nausea, vomiting, and/or diarrhoea.	YES, drugs that potentially interact with venlafaxine to produce serotonin syndrome are clearly indicated in the SmPC and PIL. The signs and symptoms of serotonin syndrome are also indicated so that patients may seek help and minimise further consequences of serotonin syndrome.
Increased pressure in the eye (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.	YES, angle-closure glaucoma is clearly indicated in the SmPC and PIL.

Hypertension	Dose-related increases in blood pressure have been commonly reported with venlafaxine. In some cases, severely elevated blood pressure requiring immediate treatment has been reported in post-marketing experience. Blood pressure changes can also impact on underlying cardiac disorders (see separate safety concern for more details).	YES, the SmPC and PL clearly indicate that commencement of treatment with venlafaxine prolonged-release tablets requires screening for high blood pressure and that pre-existing hypertension should be controlled before initiation of treatment. Blood pressure should also be monitored periodically, after initiation of treatment and after dose increases.

Risk	**What is known**	**Preventability**
Abnormality in the electrocardiogram known as QT prolongation, Torsade de Pointes, ventricular tachycardia and other fatal cardiac arrhythmias.	Changes, such as increases in heart rate can occur, particularly with higher doses and venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. In post-marketing experience, fatal cardiac arrhythmias have been reported with the use of venlafaxine, especially in overdose. Potential blood pressure changes should also be taken into account (see separate safety concern for more details).	YES, the SmPC and PL clearly indicate that there are risks of exacerbating cardiac disorders and/or patients experiencing arrhythmia during treatment. Patients and HCPs informed of the risks can weigh up the risk-benefit ratio of treatment as well as seek appropriate monitoring to avoid additional problems.
Convulsion	Convulsions are uncommon with antidepressants, but they can occur especially when antidepressants are combined with other medicines that may increase convulsions.	YES, the SmPC and PL clearly indicate that avoid the use of Venlafaxine with medicines known to trigger convulsion.
Low sodium levels (Hyponatremia)	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.	YES, the SmPC and PL clearly indicate that appropriate monitoring is necessary to avoid additional problems.
Abnormal bruising or bleeding such as bruises, nosebleeds, gastrointestinal bleeding, blood spots in the skin to life-threatening hemorrhages (Bleeding disorders)	Some studies have shown that antidepressants can increase the risk of bleeding, especially from the upper gastrointestinal tract. Venlafaxine and other antidepressants may cause patients to have an increased chance of bleeding. Taking aspirin or blood thinners may increase the risk of bleeding.	YES, the SmPC and PL clearly indicate that appropriate monitoring are necessary to avoid bleeding problems

Lipid effect (elevated cholesterol, elevated triglycerides and diseases with high levels of lipids in the blood	Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials.	YES, the SmPC and PL clearly indicate that appropriate screening and monitoring are necessary to avoid additional problems.

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 behavior (immobility and unresponsiveness to the surrounding world). Milder degrees of mania are sometimes called 'hypomania'.	YES, the SmPC and PL clearly indicate monitoring for early symptoms, to avoid additional problems
Skin reactions that can progress to produce a disease known as Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme	Stevens-Johnson syndrome and toxic epidermal necrolysis are severe diseases characterized by extensive blisters, high fever, sloughing and painful skin. If very severe, they can sometimes be life threatening and may be fatal.	YES, the SmPC and PL clearly indicate monitoring for early symptoms, to avoid additional problems
Allergic reaction known as anaphylaxis.	Hypersensitivity and allergic reactions are generally extremely rare, but still possible with any active substance or excipient, although the frequency of hypersensitivity with venlafaxine has not been accurately estimated. Anaphylactic reactions can progress to a life-threatening shock, even after the first administration. In these cases Venlafaxine prolonged-release tablets should be discontinued and suitable treatment (e.g. treatment for shock) initiated.	YES, the product should not be used in patients with known allergic reaction/ hypersensitivity to venlafaxine or the excipients. This is reflected in the SmPC and PIL. However, it cannot be prevented if allergy or hypersensitivity is not known before the first administration. In this case, the text of the SmPC indicates the measures to take.

Risk	**What is known**	**Preventability**

Interaction with other drugs: Monoamine oxidase inhibitors (MAOIs)	The development of a potentially life-threatening serotonin syndrome can occur when venlafaxine is used concomitantly with several classes of drugs in addition to drugs called monoamine oxidase inhibitors (MAOIs).	YES, drugs that potentially interact with venlafaxine to produce serotonin syndrome are clearly indicated in the SmPC and PIL. The signs and symptoms of serotonin syndrome are also indicated so that patients may seek help and minimise further consequences of serotonin syndrome due to possible drug interaction with MAOIs.

Table 51. Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Aggression including homicidal behaviour	Aggression may occur in a small proportion of patients with mood disorders who have received antidepressants, including venlafaxine. These symptoms may occur after initiation, dose changes and discontinuation of treatment. As with other antidepressants, venlafaxine should be used cautiously in patients with a history or family history of bipolar disorder or aggression. Psychiatric disorders are considered a "potential" risk due to the reduced frequency and application to a particular subset of patients.
Diabetes	In patients with diabetes, treatment with an SSRI or venlafaxine may alter glycaemic control. Insulin and/or oral antidiabetic dosage may need to be adjusted. This is considered a "potential" risk due to the unknown frequency of occurrence and application to a particular subset of patients.
Ischemic 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 behaviors 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
Lack of efficacy associated with generic substitution (the nocebo effect)	Based on data available in the post-marketing, venlafaxine may be associated with lack of efficacy, especially when switching between products with the same active substance (generic substitution). This is considered as a "potential risk" as this effect is not possible to accurately estimate and exact data on the potential mechanism are lacking. It should be highlighted that observation of the tablet in the stool is a normal property of this medicine as is not a sign of lack of efficacy.

Table 52. Missing information

Risk	**What is known**
Use in paediatric population	Venlafaxine is not recommended for use in children and adolescents. Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy and do not support the use of

Risk	**What is known**

	venlafaxine in these patients. The efficacy and safety of venlafaxine for other indications in children and adolescents under the age of 18 have not been established. Therefore the use in paediatric population is considered to be important missing information.
Use in patient with severe liver impairment	The use of venlafaxine has not been studied in patient with severe liver impairment. Therefore the use in this special population is considered to be important missing information.
Use in pregnancy and breastfeeding	Non-clinical animal studies have shown some signs of reproductive toxicity and although some suggestion of harm to the foetus (and neonate via lactation) has been observed (see separate safety concerns for more details), the safety in pregnancy has not been established. Therefore, use in pregnancy is considered to be important missing information.
Use in elderly patients	The use of venlafaxine has not been studied in elderly patients. Therefore the use in this special population is considered to be important missing information.

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 SmPC and the PL for Venlafaxine prolonged-release tablets can be found in EPAR of Venlafaxine prolonged-release tablets, available from the webpage of EMA.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

There are no studies planned in the post-authorisation development plan, so this section remains “not applicable”.

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

Version	Date	Safety Concern	Comment
1.0	18 Feb-2016	*Following safety concerns are added:* **Important identified risks:** Change -Hypercholesterolemia to Lipid effects (elevated cholesterol, elevated triglycerides and hyperlipidaemias) -Add erythema multiforme to serious skin reactions. **Important potential risks:** -Add including homicidal behaviour to Agression. **Important missing information:** Add Use in elderly patients.	This RMP has been updated according to SE/H/582/01-04/II/25 assessment report.
2.0		*Following safety concerns are added/ deleted:* **Important identified risks:** *-Add interaction with other drugs: Monoamine oxidase inhibitors (MAOIs)* **Important potential risks:** *-Delete risk associated with maternal use (including autistic disorder)*	This RMP has been updated according to SE/H/582/01-04/II/25 assessment report.