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 23. 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

Risk	What is known (Including reason why it is considered a potential risk)
	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.
Potential medication error	There are serious cases of incorrect administration, if the product features double the strength compared to the authorised/established product, also a two times higher dosage might be administered erroneously or taking double or triple doses by error.

Table 24. 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 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 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 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 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 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
0.1	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. **Missing information:** Add Use in elderly patients.	This RMP has been updated according to SE/H/582/01-04/II/25 assessment report.
0.2		*Following safety concerns are added/ deleted:* **Important identified risks:** *-Add interaction with other drugs: Monoamine oxidase inhibitors (MAOIs)* **Important potential risks:**	This RMP has been updated according to SE/H/582/01-04/II/25 assessment report.

Version	Date	Safety Concern	Comment
		-Delete risk associated with maternal use (including autistic disorder)	
0.3	06 Sep 2016	*- review CDMH: Risks associated with maternal use (including autistic spectrum disorder)*	
0.4	31 Oct 2017	No changes	Addition of 300 mg strength SE/H/0581/005/DC, SE/H/0582/005/DC, SE/H/0564/005/DC
0.5	17 April 2018	- The important identified risks: convulsions, serotonin syndrome and interactions with other drugs should be removed, according RMS.	update the RMP according to assessment conclusions made during the PSUSA procedure PSUSA/00003104/201705 (LoQ)
0.6	01 August 2018	Update the list of safety concerns according CMS NL	
0.7	03 October 2018	Special warnings and precautions for use were added at SmPC and PL	
0.8	24 October 2018	Remove SJS, TEN and EM from the list of safety concern Delete the word "important" from "Missing information"	Day 120 comments