

**PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY
PRODUCT**

Active substance (INN or common name):	Venlafaxine
Pharmaco-therapeutic group (ATC Code):	Serotonin and norepinephrine reuptake inhibitor (SNRI) Antidepressant Anxiolytic ATC code: NO6A X16
Name of Marketing Authorisation Holder or Applicant:	Pfizer
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Efexor Depot Venlafaxine Pfizer

Data lock point for RMP

05 May 2013

Version number

1.1

Date of final sign off

07 November 2013

6.1. ELEMENTS FOR SUMMARY TABLES IN THE EPAR

6.1.1. Summary Table of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Withdrawal syndrome
	Increased blood pressure/ Increased heart rate
	Lipid effects (elevated cholesterol, elevated triglycerides and hyperlipidaemias)
	Hyponatremia
	Convulsion
	Serotonin syndrome
	Suicidality
	Abnormal Bleeding: ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages
	Interactions with other drugs: Monoamine oxidase inhibitors (MAOIs) Serotonergic agents
	Mania/hypomania
	Severe cutaneous adverse reactions (SCAR) including Stevens-Johnson syndrome (SJS), Erythema multiforme (EM), and toxic epidermal necrolysis (TEN)
	Anaphylaxis
	QT prolongation/ TdP
Angle closure glaucoma	
Important potential risks	Ischemic Cardiac Events
	Diabetes
	Aggression including homicidal behavior
Important missing information	Use in elderly patients
	Use in pediatric patients
	Use in pregnant/lactating women
	Use in severe hepatic impairment

6.1.2. Table of On-going and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

There are no ongoing or planned studies at this time

6.1.3. Summary of Post Authorisation Efficacy Development Plan

There is no efficacy development plan at this time

6.1.4. Summary Table of Risk Minimisation Measures

Identified Risks

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks		
Withdrawal Syndrome	SmPC Section 4.2 Posology and method of administration, Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None
Increased Blood Pressure/Increased Heart Rate	SmPC Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None
Lipid Effects (elevated cholesterol, elevated triglycerides and hyperlipidaemias)	SmPC Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None
Hyponatremia	SmPC Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None
Convulsion	SmPC Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None
Serotonin syndrome	SmPC Section 4.4 Special Warnings and precautions; 4.5, Interaction with other medicinal products and other forms of interaction; and in Section 4.8 Undesirable effects.	None
Suicidality	SmPC Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None
Abnormal Bleeding (ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages)	SmPC Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None
Interactions with other drugs including monoamine oxidase inhibitors (MAOIs) and serotonergic agents	SmPC Section 4.3 Contraindications; Section 4.4 Special Warnings and precautions; Section 4.5 Interaction with other medicinal products and other forms of interaction; and in Section 4.8 Undesirable effects.	None
Mania/hypomania	SmPC Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None
Severe cutaneous adverse reactions including Stevens-Johnson, Erythema multiforme, and toxic	SmPC Section 4.8 Undesirable effects.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
epidermal necrolysis		
Anaphylaxis	SmPC Section 4.8 Undesirable effects.	None
QT prolongation/TdP	SmPC Section 4.8 Undesirable effects.	None
Angle closure glaucoma	SmPC Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None

Potential Risks

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important potential risks		
Ischemic Cardiac Events	SmPC Section 4.4 Special Warnings and precautions.	None
Diabetes	SmPC Section 4.4 Special Warnings and precautions.	None
Aggression including homicidal behaviour	SmPC Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None

Missing Information

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important missing information		
Use in elderly patients	SmPC Section 4.2 Posology and method of administration.	None
Use in paediatric patients	SmPC Section 4.2 Posology and method of administration, Section 4.4 Special Warnings and precautions; and in Section 4.8 Undesirable effects.	None
Use in pregnant/lactating women	SmPC Section 4.6 Pregnancy and Lactation.	None
Use in patients with severe hepatic impairment	SmPC Section 4.2 Posology and method of administration	None

6.2. ELEMENTS FOR A PUBLIC SUMMARY

6.2.1. 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 favorite 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 "counseling"), or a combination of the two. One of these medicines is Efexor Depot which contains an active substance known as venlafaxine.

Generalized Anxiety Disorder (GAD)

Generalized anxiety disorder is a severe, ongoing anxiety condition that interferes with day-to-day activities that occurs in both children and adults. GAD is similar in some ways to panic disorder, obsessive-compulsive disorder and other types of anxiety. Living with generalized anxiety disorder can be a long-term challenge. In many cases, it occurs along with other anxiety or mood disorders. In most cases, generalized anxiety disorder improves with medications, psychological counseling (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 everyday social interactions. People with SAD may often realize 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 everyday 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 counseling, 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 lifetimes, perhaps during stressful situation ends, but don't have persistent attacks.

Panic disorder is a chronic mental health condition, but treatment such as psychological counseling, 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.

6.2.2. Summary of Treatment Benefits

Efexor Depot is a prescription medicine used to treat depression, generalized 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.

Altogether, about 17,000 subjects have participated in venlafaxine studies initiated by the manufacturer. In those studies venlafaxine was shown to be effective in depression, anxiety or generalized anxiety disorder, social anxiety disorder and panic disorder.

6.2.3. Unknowns Relating to Treatment Benefits

Most of the patients in the Efexor Depot studies were white adults, but there is no evidence to suggest the medicine works any differently in patients from other racial or ethnic groups.

6.2.4. Summary of Safety Concerns

Important Identified Risks

Safety Concern	What is Known	Preventability
Symptoms when stopping desvenlafaxine (discontinuation symptoms or 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), diarrhea, seizures (convulsions).	Yes. Venlafaxine should not be discontinued suddenly. 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	In human studies, venlafaxine could increase blood pressure or worsen already existing high blood pressure (hypertension). Dose-related increases in blood pressure have been reported in some patients treated with venlafaxine. Cases of elevated blood pressure requiring immediate treatment have been reported with venlafaxine.	Yes, measurement of blood pressure is recommended for patients receiving venlafaxine. For patients with previous diagnosis of high blood pressure, the blood pressure should be controlled before starting treatment with venlafaxine.
Lipid effects (elevated cholesterol, elevated triglycerides and diseases with high levels of lipids in the blood)	Elevations in lipids including cholesterol and triglycerides were observed in human studies.	Yes, by monitoring lipids.
Low sodium levels or 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, by monitoring for early symptoms especially in elderly patients, in patients taking diuretics (fluid tablets), and in dehydrated patients.
Convulsion	Convulsions are uncommon with antidepressants, but they can occur especially when antidepressants are combined with other medicines that may increase convulsions.	Yes, by avoiding (as far as possible) the use of venlafaxine with medicines known to trigger convulsions.
Serotonin syndrome occurs because the chemical substance known as serotonin is accumulated in the body.	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), diarrhea, loss of coordination, coma,	Yes, avoiding the concomitant use of medicines that affect a substance in the body known as serotonin, and by monitoring for early symptoms of serotonin syndrome.

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

Safety Concern	What is Known	Preventability
	fast heart beat, nausea, increased body temperature, vomiting, muscle stiffness and/or confusion. Patients should tell their healthcare providers all medicines they are taking and check in advance with their healthcare providers before starting new medications.	
Suicidality	Venlafaxine is not recommended for use in children and adolescents. For young adults, antidepressant medicines may increase suicidal thoughts or actions within the first few months of treatment. 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.	Yes, by monitoring for early symptoms. Patients and caregivers should pay close attention to any changes, especially sudden changes, in mood, behaviors, 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.
Abnormal bruising or bleeding such as bruises, nosebleeds, gastrointestinal bleeding, blood spots in the skin to life-threatening hemorrhages	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, by monitoring for early symptoms. 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.	Medicines used to treat depression can have a higher effect when administered with other medicines that increase the levels of serotonin in the body.	Yes, by informing health care providers of all medicines patients are taking. Patients should not start new medicines without first checking with their healthcare provider.
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, by monitoring for early symptoms; patient should contact a health care provider.
Skin reactions that can progress to produce a disease known as Stevens-Johnson or toxic epidermal necrolysis	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, by monitoring for early symptoms; patient should contact a health care provider.

Safety Concern	What is Known	Preventability
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.	Yes, by monitoring for early symptoms; patient should immediately contact a health care provider.
Abnormality in the electrocardiogram known as QT prolongation/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.	Yes, by avoiding the use of venlafaxine in patients with cardiac conduction problems. Patients should undergo a prompt medical evaluation for any palpitations (feeling of the heart fluttering or racing).
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.	Yes, by monitoring for early symptoms. Patients with eye symptoms should seek medical care.

Important Potential Risks

Safety Concern	What is Known
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.
Diabetes	Diabetes is a disease characterized 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 behavior	Antidepressants may produce agitation and aggression in depressed patients.

Important Missing Information

Safety Concern	What is Known
Limited information on use in elderly patients	Although some people older than 65 years of age were included in the venlafaxine clinical studies, there were not sufficient number of individuals included.
Limited information on use in children	Children were not studied in the venlafaxine program.
Limited information on use in pregnant or lactating women	Animal data showed that venlafaxine can produce fetal harm, therefore it should not be used in pregnant or lactating women.
Limited information on use in patients with severe impairment of liver function	Patients with severe hepatic diseases were not studied in the venlafaxine program.

6.2.5. Summary of Additional Risk Minimisation Measures by Safety Concern

None

6.2.6. Planned Post Authorisation Development Plan

None

List of Studies in Post Authorisation Development Plan

None

Studies Which are a Condition of the Marketing Authorisation

None

6.2.7. Summary of Changes to the Risk Management Plan Over Time

Not applicable