VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Depression

Depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration. It can be long lasting or recurrent, substantially impairing a person's ability to function at work or school, or cope with daily life.

In Europe each year, about 7% of the population suffer from a major depression. This figure rises to over 25% if anxiety and lighter forms of depression are included. Mental disorders account for about 20% of the burden of disease in the European Region, rising to 26% in the countries in the European Union (EU). Depression alone is responsible for about 15% of all days lived with disability. Some countries, such as Denmark and the Netherlands, have reported that up to 50% of

long-term sick leave and disability payments are due to mental disorders, mostly depression. Depression can also lead to high blood pressure, myocardial infarction, stroke and probably, some research suggests, cancer. In turn, cardiovascular diseases, cancer and diabetes lead to an increase in depression. The combination of non-communicable diseases and risk factors is associated with higher suffering and mortality. (1)

Panic disorder and agoraphobia

Panic disorder is a severe and persistent mental disorder, associated with a high degree of subjective distress, occupational and social disability. A panic attack (PA) is the core syndrome of panic disorder and is defined as a discrete period of intense fear or discomfort accompanied by somatic and psychic symptoms, which may or may not be precipitated by exposure to a phobic stimulus. The 12-month prevalence of panic disorder and agoraphobia without history of panic were estimated to be 1.8% (0.7-2.2) and 1.3% (0.7-2.0) respectively across studies. Rates are twice as high in females and age of first onset for both disorders is in adolescence or early adulthood. In addition to comorbidity with agoraphobia, panic disorder is strongly associated with other anxiety disorders, and a wide range of somatoform, affective and substance use disorders. Even subclinical forms of panic disorder (i.e., panic attacks) are associated with substantial distress, psychiatric comorbidity and functional impairment. (2)

Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive thoughts, images, or urges (obsessions) that typically cause anxiety or distress, and by repetitive mental or behavioral acts (compulsions) that the individual feels driven to perform, either in response to an obsession or according to rules that he or she believes must be applied rigidly. OCD typically starts in childhood or adolescence, persists throughout a person's life, and produces substantial impairment in functioning due to the severe and chronic nature of the illness.

OCD is associated with substantial comorbidity, not only with anxiety and mood disorders but also with impulse-control and substance use disorders. Lifetime and 12-month prevalence estimates for DSM-IV OCD are 2.3% and 1.2%, respectively. Males make up the majority of very early onset cases, with nearly a quarter of males having onsets before age 10. In contrast, females have a much more rapid accumulation of new cases after age 10, with the highest slope during adolescence. The

most common comorbid conditions are anxiety disorders, followed by mood disorders, impulse-control disorders, and substance use disorders. [3]

Social anxiety disorder

The fundamental feature of social anxiety disorder is the marked and persistent fear of social or performance situations in the presence of unfamiliar people or when scrutiny by others is possible, even in the context of small groups. Exposure to such social and performance situations almost invariably provokes an immediate anxiety response or avoidance behaviour. Associated features of social anxiety disorder frequently include poor social skills, hypersensitivity to criticism and negative evaluation, difficulty of being assertive as well as low self-esteem and feelings of inferiority. Epidemiologic surveys conducted across Europe indicate that the lifetime prevalence of social anxiety disorder in the general population is close to 7%. Patients with a primary diagnosis of social anxiety disorder generally also manifest symptoms associated with depression, other anxiety disorders, or alcohol/substance abuse. In many cases, the co-occurring symptomatology is sufficient to meet diagnostic criteria for other conditions, and it has been estimated that 70 to 80% of subjects with social anxiety disorder have at least one other psychiatric disorder. The co-morbid disorders consistently reported with social anxiety disorder are major depression, phobic disorders and alcohol and substance abuse disorders.[4]

Post-traumatic stress disorder (PTSD)

PTSD develops after a terrifying ordeal that involved physical harm or the threat of physical harm. The person who develops PTSD may have been the one who was harmed, the harm may have happened to a loved one, or the person may have witnessed a harmful event that happened to loved ones or strangers. PTSD was first brought to public attention in relation to war veterans, but it can result from a variety of traumatic incidents, such as mugging, rape, torture, being kidnapped or held captive, child abuse, car accidents, train wrecks, plane crashes, bombings, or natural disasters such as floods or earthquakes.

A potentially traumatic event (PTE) contributes to trauma through its frequency, conditional probability of posttraumatic stress disorder (PTSD), and experience of other PTEs. A cross-sectional survey was conducted, enrolling 21,425 adults nationally representative of six European countries. Using the WHO-Composite International Diagnostic Interview, 8,797 were interviewed

on 28 PTEs and PTSD. Prevalence of 12-month PTSD was 1.1%. When PTSD was present, the mean number of PTEs experienced was 3.2. In a multivariate analysis on PTEs and gender, six PTEs were found to be more traumatic, and to explain a large percentage of PTSD, as estimated by their attributable risk of PTSD: rape, undisclosed private event, having a child with serious illness, beaten by partner, stalked, beaten by caregiver.(5)

VI.2.2 Summary of treatment benefits

Major Depressive Disorder

Sertraline was compared with a placebo (a dummy treatment) in a study involving depressed outpatients who had responded by the end of an initial 8-week open treatment phase on sertraline 50-200 mg/day. These patients were randomized to continuation for 44 weeks on double-blind sertraline 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking sertraline compared to those on placebo. The mean dose for completers was 70 mg/day. The % of responders (defined as those patients that did not relapse) for sertraline and placebo arms were 83.4% and 60.8%, respectively.(6)

Post traumatic stress disorder (PTSD)

Combined data from the 3 studies of PTSD in the general population found a lower response rate in males compared to females. In the two positive general population trials, the male and female sertraline vs. placebo responder rates were similar (females: 57.2% vs 34.5%; males: 53.9% vs 38.2%). The number of male and female patients in the pooled general population trials was 184 and 430, respectively and hence the results in females are more robust and males were associated with other baseline variables (more substance abuse, longer duration, source of trauma etc) which are correlated with decreased effect.(6)

Paediatric OCD

The safety and efficacy of sertraline (50-200 mg/day) was examined in the treatment of nondepressed children (6-12 years old) and adolescent (13-17 years old) outpatients with obsessive compulsive disorder (OCD). After a one week single blind placebo lead-in, patients were randomly assigned to twelve weeks of flexible dose treatment with either sertraline or placebo. Children (6-12 years old) were initially started on a 25 mg dose. Patients randomized

to sertraline showed significantly greater improvement than those randomised to placebo on the Children's Yale-Brown Obsessive Compulsive Scale CY-BOCS (p =0.005) the NIMH Global Obsessive Compulsive Scale (p=0.019), and the CGI Improvement (p =0.002) scales. In addition, a trend toward greater improvement in the sertraline group than the placebo group was also observed on the CGI Severity scale (p=0.089). For CY-BOCs the mean baseline and change from baseline scores for the placebo group was 22.25 ± 6.15 and -3.4 ± 0.82, respectively, while for the sertraline group, the mean baseline and change from baseline scores were 23.36 ± 4.56 and -6.8 ± 0.87, respectively. In a post-hoc analysis, responders, defined as patients with a 25% or greater decrease in the CY-BOCs (the primary efficacy measure) from baseline to endpoint, were 53% of sertraline-treated patients compared to 37% of placebo-treated patients (p=0.03).[(6)]

These studies were conducted for Lustral by Pfizer and not by Mylan.

VI.2.3 Unknowns relating to treatment benefits

Efficacy is not shown in paediatric major depressive disorder. Long term efficacy data are lacking in non-depressed children (6-12 years old) and adolescent (13-17 years old) with obsessive compulsive disorder (OCD). No data is available for children under 6 years of age.

VI.2.4 Summary of safety concerns

Table 24 Part VI - Summary table of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Serotonin Syndrome	Possible side effects include: agitation, confusion, diarrhoea, high temperature and blood pressure, excessive sweating and rapid heartbeat.	Yes, by monitoring for early symptoms. If you notice any of these symptoms while taking sertraline, consult your

Risk	What is known	Preventability
		doctor or seek medical help immediately.
Suicidality	Possible side effects include: depressive symptoms with suicidal ideas and suicidal behaviours	Yes, by monitoring for early symptoms. If you notice any of these symptoms, consult your doctor or medical help immediately.
Abnormal bleeding/ haemorrhage	Possible side effects include: bleeding problems (such as nose bleed, stomach bleeding, or blood in urine), excessive vaginal bleeding.	Yes, by monitoring for early symptoms. If you notice any of these symptoms while taking sertraline, consult your doctor or medical help immediately.
Bone fractures	An increased risk of bone fractures has been observed in patient's taking sertraline.	Yes, an increased risk of bone fractures has been observed in patients taking this type of medicines. Physicians should be aware about this possible risk and administer the drug with caution in patients at the risk:
Hyponatraemia (low blood sodium levels)	Hyponatraemia appears to be the result of a syndrome called inappropriate antidiuretic hormone secretion (SIADH), which has been observed with increased frequency in patients treated with sertraline	Physicians should be aware about this possible risk and should administer the drug with caution especially in patients receiving certain medicines for hypertension and the elderly patients.

Risk	What is known	Preventability
	and other medicines of the same class. Elderly patients and patients treated with diuretics (water medication) are more prone to experience such event. Signs and symptoms: headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.	
Convulsions (fits)	Sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.	Yes, by monitoring for early symptoms. If you experience seizures, consult your doctor or medical help immediately.

Important potential risk:

Risk	What is known (Including reason why it is considered a potential risk)
Use in pregnancy	If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine, because the safety of sertraline has not fully been established in pregnant women. Sertraline should only be given to pregnant women if the doctor considers that the benefit for the mother exceeds any possible risk to the foetus. Women of childbearing potential should employ an adequate method of contraception if taking sertraline. In case patients have taken sertraline throughout pregnancy, they should make sure they inform the midwife and/or doctor. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like sertraline may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately. Your newborn baby might also have other conditions, which usually begin during the first 24 hours after birth. Symptoms include: trouble with breathing, a blueish skin or being too hot or cold, blue lips, vomiting or not feeding properly, being very tired, not able to sleep or crying a lot, stiff or floppy muscles, tremors, jitters or fits, increased reflex reactions, irritability and low blood sugar. If your baby has any of these symptoms when it is born, or you are concerned about your baby's health, contact your doctor or midwife who will be able to advise you.

Diabetes mellitus	In patients with diabetes, treatment with sertraline may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted. Diabetes mellitus was reported in patients using sertraline with not known frequency.

Missing information:

Risk	**What is known (Including reason why it is considered missing information)**
Limited information on use in children under 6 years of age	There is no data available regarding the administration of sertraline to children under less than six years of age.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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. The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned.

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

RMP version 1.0 was updated to version 2.0 (this document), in line with the RMS Day 70 Preliminary Assessment Report for Sertraline Vale, film coated tablets 50mg & 100mg, procedure number DK/H/2631/001-002/DC, by Applicant Vale Pharmaceuticals Limited.