PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Important identified risks	• Serotonin syndrome • Suicidality
Important potential risks	• Diabetes mellitus • Use in pregnancy • Abnormal bleeding/ haemorrhage
Missing information	• Use in paediatric patients, especially under age of 6 years

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risk: Serotonin syndrome	Sections 4.3, 4.4, 4.5 and 4.8 of proposed sertraline SmPC have information on this safety concern. Other routine risk minimisation measure includes the "prescription only" status of the product.	Currently available data does not support the need for additional risk minimization activities.
Important identified risk: Suicidality	Sections 4.4 and 4.8 of proposed sertraline SmPC have information on this safety concern. Other routine risk minimisation measure includes the "prescription only" status of the product.	Currently available data does not support the need for additional risk minimization activities.
Important potential risk: Diabetes mellitus	Sections 4.4 and 4.8 of proposed sertraline SmPC have information on this safety concern. Other routine risk minimisation measure includes the "prescription only" status of the product.	Currently available data does not support the need for additional risk minimization activities.
Important potential risk: Use in pregnancy	Sections 4.6 and 5.3 of proposed sertraline SmPC have information on this safety concern. Other routine risk minimisation measure includes the	Currently available data does not support the need for

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	"prescription only" status of the product	additional risk minimization activities.
Important potential risk: Abnormal bleeding/ haemorrhage	Sections 4.4, 4.5 and 4.8 of proposed sertraline SmPC have information on this safety concern. Other routine risk minimisation measure includes the "prescription only" status of the product.	Currently available data does not support the need for additional risk minimization activities.
Missing information: Use in paediatric patients, especially under age of 6 years	Sections 4.2, 4.4 and 5.1 of proposed sertraline SmPC have information on this safety concern. Other routine risk minimisation measure includes the "prescription only" status of the product.	Currently available data does not support the need for additional risk minimization activities.

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Major depressive episodes and Prevention of recurrence of major depressive episodes (MDE):

The World Health Organization ranks depression as the fourth leading cause of disability worldwide and projects that by 2020, it will be the second leading cause. Data from 18 countries were analyzed. The average lifetime and 12-month prevalence estimates of MDE were 14.6%

and 5.5% in the ten high-income and 11.1% and 5.9% in the eight low- to middle-income countries. Although rates of depression in women and men are highest in those aged 25-44 years, the incidence of clinically significant depressive symptoms increases with advancing age, especially when associated with medical illness or institutionalization. The female: male ratio was about 2:1. In high-income countries, younger age was associated with higher 12-month prevalence; by contrast, in several low- to middle-income countries, older age was associated with greater likelihood of MDE. MDE is a significant public-health concern across all regions of the world and is strongly linked to social conditions.

Panic disorder with or without agoraphobia:

Panic disorder with agoraphobia is an anxiety disorder in which a person has attacks of intense fear and anxiety. There is also a fear of being in places where it is hard to escape, or where help might not be available. Agoraphobia usually involves fear of crowds, bridges, or of being outside alone. Panic with agoraphobia may be a more severe variant of panic disorder. Anxiety disorders are by far the most common psychiatric disorders (25%), followed by major depression (17%). Lifetime prevalence rates for all anxiety disorders lumped together are 19.2% for men, 30.5% for women. Panic attacks are almost twice as common in women. The age at onset of panic disorder in general is in the mid-twenties, with hazard rates for women ranging from 25 to 35 years, for men between 30 and 45 years.

Social anxiety disorder (SAD):

Social phobia or Social anxiety disorder is a strong fear of being judged by others and of being embarrassed. The median lifetime prevalence is 6.65% and high 12-month prevalence is 2–3%. The distribution of social phobia varied considerably across the countries surveyed. Prevalence rates were lower in Finland than in its Scandinavian neighbours Norway and Sweden. In American and European community studies, an increased risk of suicidality has been reported in patients with social phobia. Younger individuals showed the highest rates, and women were more frequently affected than men. Social phobia was shown to be a persistent condition with a remarkably high degree of another medical problems, associated impairment and disability.

Post traumatic stress disorder (PTSD):

Different groups have different levels of exposure to traumatic events; the conditional probability of developing PTSD following a similar level of exposure may also vary across cultural groups. Rates of PTSD are higher among veterans and others whose vocation increases the risk of traumatic exposure (e.g., police, fire-fighters, emergency medical personnel). Highest rates (ranging from one-third to more than one-half of those exposed) are found among survivors of rape, military combat and captivity, and ethnically or politically motivated internment and genocide. The prevalence of PTSD may vary across development; children and adolescents, including preschool children, generally have displayed lower prevalence following exposure to serious traumatic events; however, this may be because previous criteria were insufficiently developmentally informed.

Obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years:

The major feature of this disorder is the presence of recurring obsessions, recurrent unwanted thoughts, compulsions, and repetitive excessive actions that interfere with a person's life. Surveys have revealed the startling fact that obsessive-compulsive disorder has a lifetime prevalence rate as high as 2% to 3% and a 6-month prevalence rate of 1.6%. Obsessive-compulsive disorder often begins at an early age with a third or more cases starting at puberty. It can also begin in childhood; cases in children as young as 3 or 4 years have been reported. Male patients outnumber female patients in these very early onset cases. Overall, the illness affects both sexes about equally, with a slight preponderance of women. The disorder rarely begins after age 40. No specific predictors of treatment outcome have been identified for pediatric obsessive-compulsive disorder.

VI.2.2 Summary of treatment benefits

Sertraline is used to treat depression (major depressive episodes) and anxiety disorders (such as panic disorder with or without agoraphobia, post traumatic stress disorder and social anxiety

disorder in adults and obsessive-compulsive disorderin adults and children and adolescents aged 6-17 years old).

Major depressive episodes

A study was conducted which involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase to sertraline 50-200 mg/day. These patients were continuation in study for 44 weeks on sertraline 50-200 mg/day or placebo. . The mean dose for completers was 70 mg/day. A statistically significantly lower relapse rate was observed for patients taking sertraline compared to those on placebo.

Obsessive-compulsive disorder

The safety and efficacy of sertraline (50-200 mg/day) was examined in the treatment of non-depressed children (6-12 years old) and adolescent (13-17 years old) outpatients with obsessive compulsive disorder. Children (6-12 years old) were initially started on a 25 mg dose. Patients randomized to sertraline showed significantly greater improvement. In addition, a trend toward greater improvement in the sertraline group than the placebo group was also observed.

Post traumatic Stress Disorder

Combined data from 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. 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 which are correlated with decreased effect.

VI.2.3 Unknowns relating to treatment benefits

No data is available for children, especially under 6 years of age.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Serotonin syndrome	In rare cases serotonin syndrome may occur if a patient is taking certain medicines at the same time as sertraline. The symptoms would include agitation, confusion, diarrhoea, high temperature and blood pressure, excessive sweating and rapid heartbeat.	Yes The patient should inform the doctor immediately on experiencing any of these symptoms. The patients are advised to inform the doctor all the medications they are taking.
Ideas of harming or killing yourself (Suicidality)	The patient may experience depressive symptoms with ideas of harming or killing yourself, or Suicide/suicidal thoughts/suicide attempts or clinical worsening.	Yes The patient should inform the doctor immediately on noticing any of the side effects.

Important potential risks

Risk	What is known
Diabetes mellitus	Take special care with Sertraline Tablets: Your blood glucose levels may be altered due to Sertraline Tablets and your diabetes medicines may need to be adjusted. Talk to your doctor if you are taking the following medicine: Medicines to treat diabetes (tolbutamide).

Risk	**What is known**
	After marketing sertraline, the following side effects have been reported: Problems controlling blood sugar levels (diabetes), increase in blood sugar levels
Use in pregnancy	Ask your doctor or pharmacist for advice before taking any medicine. The safety of sertraline has not fully been established in pregnant women. Sertraline will only be given to you when pregnant if your doctor considers that the benefit for you is greater than any possible risk to the developing baby. If you are a woman capable of having children you should use a reliable method of contraception (such as the contraceptive pill), when taking sertraline. Make sure your midwife and/or doctor know you are on Sertraline Tablets. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like Sertraline Tablets 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 bluish skin or being too hot or cold, • blue lips,

Risk	What is known
	• 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, • 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.
Abnormal bleeding/ Haemorrhage	Bleeding problems (such as nose bleed, stomach bleeding, or blood in urine) have been reported with sertraline. Inform the doctor immediately if any of these signs occur during treatment

Missing information

Risk	What is known
Use in paediatric patients, especially under age of 6 years	No data is available for children under 6 years of age. Sertraline should not usually be used in children and adolescents less than 18 years old, except for patients with obsessive compulsive disorder (OCD). Patients under 18 years have an increased risk of undesirable effects, such as suicide attempt, thoughts of harming or killing themselves (suicidal thoughts) and hostility (mainly aggressiveness, oppositional behaviour and anger)

Risk	What is known
	when they are treated with this class of medicines. Nevertheless, it is possible that your doctor decides to prescribe sertraline tablets to a patient under 18 years if it is in the patient's interest. If your doctor has prescribed Sertraline Tablets to you and you are less than 18 years old and you want to discuss this, please contact him/her. Furthermore, if any of the symptoms listed above appear or worsen while you are taking Sertraline Tablets, you should inform your doctor. Also, the long-term safety of Sertraline Tablets in regard to growth, maturation and learning (cognitive) and behavioural development in this age group has not yet been demonstrated.

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.

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

Version	Date	Safety Concern	Comment
5.0	10 November 2015	No changes in safety concerns	RMP has been updated based upon Day 145 comment received from Italy (IT), dated 04-Nov-2015. SmPC and PIL has been updated
4.0	06 July 2015	Following safety concerns are deleted: **Important Identified risks:** • Neuroleptic malignant syndrome • Hyponatremia • Withdrawal symptoms • Angle closure glaucoma • Akathisia **Important Identified risks:** • Possible increased risk of male infertility due to sperm impairment • Cardiovascular disorders • Concomitant use of St John's Wort • Concomitant use with drugs metabolised by CYP2D6	RMP has been updated based upon RMS Day 70 Preliminary Assessment Report (NL/H/3385/001-002/DC) dated 28 April 2015. Product overview is shorten, reference in summary table removed, and summary table of risk minimisation measures is updated with section numbers of SmPC.

Version	Date	Safety Concern	Comment
		Isoenzymes • Activation of mania • Seizure in patients with epilepsy • PPHN in newborn • Bone fracture in the elderly **Missing information:** • Severe hepatic impairment - Abnormal bleeding/haemorrhage is changed from important identified risk to important potential risk.	
3.0	02 December 2014	- No changes in safety concerns	RMP updated as per request for further information by agency (PL 20075-0067-0068)dated 28-Nov-2014
2.0	07 Nov 2014	Following safety concerns are added: **Important potential risks:** • Cardiovascular disorders • Concomitant use of St Johns Wort • Concomitant use with drugs	Safety concerns and Part VI.2.4"Summary of safety concerns", Part IV "Plans for post-authorisation efficacy studies" and part VI "Summary of the risk management

Version	Date	Safety Concern	Comment
		metabolised by CYP2D6 isoenzymes • Activation of mania • Seizure in patients with epilepsy • Pregnancy • PPHN in newborn • Diabetes • Bone fracture in the elderly Missing information: • Severe Hepatic impairment	plan by product" have been updated as per comments given in Type II Preliminary Variation Assessment Report for Sertraline 50mg and 100mg Film coated tablets (PL 20075/0067 - 0036) dated 22 Sep 2014.