VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Depression is an illness in which feeling of sadness or lack of interest in most activities is present persistently (almost every day). Together with at least one of the above mentioned core symptoms, a person can be diagnosed as having depression if any four of the following symptoms are also present:

- loss of energy,
- sleepiness or poor sleep,
- feelings of guilt,
- change in appetite,
- poor concentration,
- irritability or frustration,
- repeated thoughts of death or suicide or suicide attempt.

Symptoms should have been present persistently for at least 2 weeks and must have resulted in significant distress and impairment in functioning. Patients may experience only a single or multiple episodes of depression during their lifetime.

Depression is a common disorder. In a study involving 6 European countries (Belgium, France, Germany, Italy, the Netherlands, and Spain), overall, 13 in 100 persons were found to have depression at some point in their lives. Women were reported to be more commonly affected than men. In the same study, 17 in 100 women and 9 in 100 men had depression during their lifetime. In the US, a household survey estimated that 17 in 100 patients had depression during their lifetime. The age group most commonly affected was the 30 to 44 years age group; 20 in 100 persons had depression in this age group.

VI.2.2 Summary of treatment benefits

The efficacy of mirtazapine as a treatment for major depressive disorder was established in 4 placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depressive disorder. Patients were titrated with mirtazapine from a dose range of 5 mg up to 35 mg/day. Overall, these studies demonstrated mirtazapine to be superior to placebo.

In a longer-term study, patients meeting (DSM-IV) criteria for major depressive disorder who had responded during an initial 8 to 12 weeks of acute treatment on mirtazapine were randomized to continuation of mirtazapine or placebo for up to 40 weeks of observation for relapse. Patients receiving continued mirtazapine treatment experienced significantly lower relapse rates over the subsequent 40 weeks compared to those receiving placebo.

VI.2.3 Unknowns relating to treatment benefits

Mirtazapine was tested in children in two studies, and it was not found to be effective in children and adolescents. Therefore, mirtazapine should not be used in children and adolescents (patients less than 18 years of age). There is limited clinical information on the use of mirtazapine during pregnancy and breast-feeding.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Weight increased and increase in appetite	In clinical trials, approximately 1 in 6 patients treated with mirtazapine experienced increased appetite, and 1 in 8 experienced weight gain. About half of the patients with weight gain increased their body weight by 7% or more.	Patients should monitor weight regularly. Proper diet should be followed and healthy levels of physical activity should be maintained.

Risk	What is known	Preventability
Elevated liver enzymes (Elevations in serum transaminases)	Increased liver enzymes may be a sign of injury to liver cells. In clinical trials, fewer than 1 in 1000 patients treated with mirtazapine had mild increases in liver enzyme levels in the blood. Most of the patients did not feel any symptoms, and the abnormal blood tests resolved promptly.	Elevated liver enzymes occur rarely and are generally mild and temporary. Jaundice (yellowing of the skin and eyes) may be a sign of severe liver injury, and mirtazapine should be stopped if jaundice occurs.

Risk	What is known	Preventability
Sleepiness and tiredness (Sedation, somnolence and lethargy, fatigue)	Sleepiness and tiredness were common (approximately half of patients treated with mirtazapine) in the clinical trials. These symptoms may interfere with a person's ability to drive a car or operate heavy machinery safely. Taking mirtazapine with other medicines that also cause sleepiness (such as sleeping pills, pain killers, and some antihistamines) may worsen this effect. Taking alcohol and mirtazapine together may enhance the effects of alcohol on the brain.	Mirtazapine should be taken at bedtime. Patients should avoid driving or operating machines while taking mirtazapine. Care should be taken if mirtazapine is used together with alcohol or medicines that produce sedation.

Risk	What is known	Preventability
Low blood pressure with changes in posture, dizziness and fainting (Orthostatic hypotension, including dizziness, syncope)	In the studies, decreases in blood pressure during changes of posture occurred infrequently. Small blood pressure decreases may not cause any symptoms, but more severe decreases may cause dizziness, or fainting. Patients with chronic vascular diseases (such as heart disease, or stroke), or who are taking medicines to treat high blood pressure, may be more vulnerable to the effects of blood pressure changes.	Patients should inform their doctors if they are taking any blood pressure-lowering medicines or have any of the risk factors for orthostatic hypotension before starting treatment with mirtazapine. Taking mirtazapine at bedtime can help avoid the unwanted consequences of orthostatic hypotension.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Abnormal heart rhythm (QT prolongation and/or ventricular arrhythmias, e.g. Torsades de Pointes)	Some medicines used to treat depression can cause changes in the conduction of electrical impulses through the heart. This may result in abnormalities of the electrocardiogram, and in rare cases, abnormal heart rhythms. Abnormal electrocardiograms, and in rare instances, abnormal heart rhythms (including a rare but serious abnormal rhythms called "torsade de pointes") have been reported in patients using mirtazapine. However, in most of these reports, the patients either overdosed, or had other factors that can cause abnormal heart rhythms (such as other medications, or underlying heart diseases). Electrocardiograms collected during the clinical trials did not show any effects. Therefore, it is not known whether mirtazapine can affect the heart rhythm.

Risk	What is known (Including reason why it is considered a potential risk)
Low level of white blood cells (Agranulocytosis and severe neutropenia)	Some medicines used to treat depression can decrease the numbers of white blood cells (WBC). When levels of white blood cells become too low, a person is at increased risk of infections. A small number of patients developed low WBC counts during clinical trials of mirtazapine, and some of them developed

Risk	What is known (Including reason why it is considered a potential risk)
	infections. When the frequency of low WBC counts in patients treated with mirtazapine was compared to that in patients who received placebo (a study treatment that contains no active medication), there was no difference. Based on information that is currently available, it is not known whether mirtazapine can affect WBC levels.

Risk	What is known (Including reason why it is considered a potential risk)
Withdrawal symptoms (Discontinuation symptoms)	Some medicines used to treat depression can cause symptoms that occur after the medicine is stopped (withdrawal symptoms). Common withdrawal symptoms include dizziness, anxiety/agitation, stomach upset and headache. Rare cases of withdrawal symptoms have been reported in patients using mirtazapine. Most of the symptoms were mild, and resolved promptly. The nature of the reported symptoms makes it difficult to determine whether they are due to medication effects, or to the depression itself. The clinical trials do not suggest that withdrawal symptoms occur frequently following mirtazapine discontinuation. While it is not certain that mirtazapine causes withdrawal symptoms, it is recommended to discontinue mirtazapine treatment gradually, rather than abruptly.

Risk	What is known (Including reason why it is considered a potential risk)
Severe skin rashes (Severe skin reactions)	Rare cases of serious skin reactions have been reported in patients using mirtazapine, including rare but potentially life-threatening rashes such as Stevens-Johnson syndrome. The reported cases were poorly documented, and often described other factors that can cause serious skin rashes (such as other medications or infections). There were no cases of serious skin reactions in the clinical trials. Therefore, it is not known whether mirtazapine can cause serious skin reactions.

Missing information

None.

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 Summary of Product Characteristics and the Package leaflet for [invented name] can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Version	**Date**	**Safety Concerns**	**Comment**
1.1	9.1.2014	Important identified risks: • Concomitant use with monoamine oxidase (MAO) inhibitors and other serotonergic medicinal products • Bone marrow depression • Seizures • Withdrawal effects • Worsening of psychiatric symptoms (including manic episodes) • Altered glycaemic control in diabetic patients • Anticholinergic effects • Akathisia/psychomotor restlessness • Hyponatraemia Important potential risks: • Use in children and adolescents under 18 years of age • Suicide/suicidal thoughts or clinical worsening • Use in patients with	Initial version.

Version	Date	Safety Concerns	Comment
		renal impairment • Use in patients with hepatic impairment • Use during pregnancy, including potential persistent pulmonary hypertension in the newborn Missing information: • Effects on fertility	
Version 2	Current version	Important identified risks: • Weight increased and increase in appetite • Elevations in serum transaminases • Sedation, somnolence and lethargy, fatigue • Orthostatic hypotension (including dizziness, syncope) Important potential risks: • QT prolongation and/or ventricular arrhythmias (e.g. Torsades de Pointes) • Agranulocytosis and severe neutropenia • Discontinuation symptoms • Severe skin reactions Missing information: None.	Updated according to EU PSUR Work Sharing Summary Assessment Report NL/H/PSUR/0006/003.

Version	Date	Safety Concerns	Comment