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

Summary of safety concerns	
Important identified risks	• Hepatotoxic reactions • Interactions with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)
Important potential risk	• Suicide
Missing information	• Use in paediatric population (<18 years) • Use in elderly (≥75 years) • Use during pregnancy • Use during lactation • Use in patients with severe or moderate renal impairment

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 RISKS		
Hepatotoxic reactions	Posology in section 4.2 of the SmPC. Contraindication in section 4.3 of the SmPC. Warning in section 4.4 on liver injury, including hepatic failure. Close surveillance of monitoring of liver function is described. Hepatobiliary disorders listed in section 4.8 of the SmPC.	Physician's guide to prescribing. Patient's booklet.
Interactions with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)	Contraindication in section 4.3 of the SmPC. Information on important interactions is presented in section 4.5 of the SmPC.	Physician's guide to prescribing.
IMPORTANT POTENTIAL RISK		

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Suicide	Warning in section 4.4 to monitor patients since depression is associated with an increased risk of suicide and suicidal thoughts. Suicidal thoughts or behaviour is listed in section 4.8 of the SmPC.	None proposed.
MISSING INFORMATION		
Use in paediatric population (<18 years)	Agomelatine is indicated in adults, in section 4.1 of the SmPC. Posology warning in section 4.2 of the SmPC. Warning in section 4.4 of the SmPC on the reported events in clinical trials with paediatric patients.	None proposed.
Use in elderly (≥75 years)	Posology warning in section 4.2 of the SmPC. Warning in section 4.4 of the SmPC on agomelatine efficacy in elderly (≥75 years).	None proposed.
Use during pregnancy	Information on the lack of safety data of agomelatine use in pregnant woman in section 4.6 of the SmPC.	None proposed.
Use during lactation	Information on the lack of safety data of agomelatine use in breastfeeding woman in section 4.6 of the SmPC.	None proposed.
Use in patients with severe or moderate renal impairment	Information on the limited clinical data in patients with severe or moderate renal impairment in section 4.2 of the SmPC.	None proposed.

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Major depression is a condition in which patients have mood disturbances that interfere with their everyday life. Symptoms often include deep sadness, feelings of worthlessness, loss of interest in favourite activities, sleep disturbances, a feeling of being slowed down, feelings of anxiety and changes in weight. The lifetime incidence of major depressive disorder in the United States is 20% in women and 12% in men. The incidence of depression was 0.9% in preschool-aged children, 1.9% in school-aged children, and 4.7% in adolescents. Social class is also a significant factor. As income decreased, the average prevalence of depression increased.

VI.2.2 Summary of treatment benefits

Based on the available data from reference product clinical studies and clinical experience of several years, agomelatine represents an effective drug in the treatment of major depressive episodes in adults.

If administered as indicated in the Summary of Product Characteristics and taking into account the contraindications, the warnings and precautions, agomelatine can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

The populations where experience is limited are reflected in the SmPC as follows: paediatric population <18 years (not recommended for use in children and adolescents), elderly ≥75 years (should not be used in this age group), pregnancy (it is preferable to avoid the use during pregnancy), lactation (it is not known if agomelatine and its metabolites are excreted into human milk, the treating physician should make a decision on discontinuation of treatment), hepatic impairment (agomelatine is contraindicated in patients with hepatic impairment), and severe or moderate renal impairment (caution should be exercised when prescribing agomelatine to this group of patients).

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Serious liver problems (hepatotoxic reactions)	Agomelatine affects the liver. Hepatic failure (few cases resulting in liver transplantation or death), elevations of liver enzymes, hepatitis and jaundice have been reported in patients treated with agomelatine. Most of them occurred during the first weeks of treatment.	Prior to treatment start, the doctor should check if the patient's liver is working properly and do so periodically during treatment. Patients whose liver is not working properly should not use agomelatine. Patients using medicines known to affect the liver should contact their doctor. The patients should be vigilant about signs and symptoms of liver problems. If the doctor increases agomelatine dose, liver tests should be repeated.
Use of medicines which modify agomelatine dose in the blood (Interactions with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin))	Agomelatine should not be used in patients taking medicines which slow down the breakdown of agomelatine in the body.	The doctor should check if the patient is using fluvoxamine or ciprofloxacin.

Important potential risk

Risk	What is known (Including reason why it is considered a potential risk)
Suicide	Patients who are depressed can sometimes have thoughts of harming or killing themselves. This may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer. This is more likely if the patient has had previous thoughts about killing or harming himself. Clinical trials have shown an increased risk of suicidal behaviour in young adults with psychiatric conditions, who were being treated with an antidepressant.

Missing information

Risk	What is known
Limited information on use in children <18 years old	The efficacy and safety of agomelatine has not been established in this population. Agomelatine is not recommended for use in children and adolescents.
Limited information on use in elderly patients ≥75 years	The efficacy and safety of agomelatine has been established in elderly depressed patients (<75 years). No effect is documented in patients ≥75 years, therefore agomelatine should not be used by this age group.
Limited information on use in pregnant women	The efficacy and safety has not been studied in this population. It is preferable to avoid the use of agomelatine during pregnancy.
Limited information on use in breastfeeding women	It is not known whether agomelatine and its metabolites are excreted in human milk. The treating physician should make a decision on discontinuation of treatment.
Limited information on use in patients with severe or moderate kidney impairment	Only limited data on the use of agomelatine in patients with severe or moderate kidney impairment is available. Therefore, caution should be exercised when prescribing agomelatine to these patients.

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 Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

In addition, this medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Serious liver problems (hepatotoxic reactions)

Risk minimisation measures: Physician's guide to prescribing and Patient's booklet
Objective and rationale: Agomelatine affects the liver. Hepatic failure and cases resulting in liver transplantation and death have been reported. For HCPs to minimise the occurrence and the severity of serious liver problems. For patients to improve their awareness of the necessity of monitoring liver functions during treatment.
Summary description of main additional risk minimisation measures – Physician's guide to prescribing and Patient's booklet to highlight the risk of serious liver problems and emphasise the necessity to monitor liver functions during agomelatine treatment
Proposed action: ➢ Physician's guide to prescribing to be provided to doctors and Patient's booklet to be provided to patients

Use of medicines which modify agomelatine dose in the blood (Interactions with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin))

Risk minimisation measures: Physician's guide to prescribing
Objective and rationale: To inform HCPs that agomelatine should not be prescribed with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).
Summary description of main additional risk minimisation measures – Physician's guide to prescribing should remind HCPs to avoid co-prescription with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).
Proposed action: ➢ Physician's guide to prescribing to be provided to doctors

VI.2.6 Planned post-authorisation development plan

Not applicable.

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

Not applicable for pre-approval versions.