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

Table 10 Summary table of safety concerns

Summary of safety concerns	
Important identified risks	• Risk of hepatotoxicity • Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)
Important potential risks	• Risk of suicidal ideation/suicides
Missing information	• Use in patients with severe or moderate renal impairment • Use in paediatric population • Use in elderly patients • Use during pregnancy and lactation

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

Table 11 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Risk of hepatotoxicity	Proposed text in SmPC: Posology and method of administration in section 4.2 Contraindications in section 4.3 Special warnings and precautions for use in section 4.4 Undesirable effects listed in section 4.8 Pharmacokinetic properties listed in section 5.2 Prescription only medicine	Educational material in the form of a prescriber's guide and patient booklet

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)	Proposed text in SmPC: Contraindications in section 4.3 Special warnings and precautions for use in section 4.4 Interaction with other medicinal products and other forms of interaction in section 4.5 Pharmacokinetic properties listed in section 5.2 Prescription only medicine	Educational material in the form of a prescriber's guide and patient booklet
Risk of suicidal ideation/suicides	Proposed text in SmPC: Special warnings and precautions for use in section 4.4 Undesirable effects listed in section 4.8 Prescription only medicine	None proposed
Use in patients with severe or moderate renal impairment	Proposed text in SmPC: Posology and method of administration in section 4.2 Pharmacokinetic properties listed in section 5.2 Prescription only medicine	None proposed
Use in paediatric population	Proposed text in SmPC: Posology and method of administration in section 4.2 Special warnings and precautions for use in section 4.4 Interaction with other medicinal products and other forms of interaction in section 4.5 Pharmacodynamic properties listed in section 5.1 Prescription only medicine	None proposed
Use in elderly patients	Proposed text in SmPC:	None proposed

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	Posology and method of administration in section 4.2 Special warnings and precautions for use in section 4.4 Pharmacodynamic properties listed in section 5.1 Pharmacokinetic properties listed in section 5.2 Prescription only medicine	
Use during pregnancy and lactation	Proposed text in SmPC: Fertility, pregnancy and lactation in section 4.6 Preclinical safety data listed in section 5.3 Prescription only medicine	None proposed

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Depressive disorders are serious psychological diseases, which are widespread, of early onset, with a risk of chronification, frequent comorbidities, including alcohol abuse, cardiovascular diseases, suicidal tendencies, and aggressive behaviour, along with decreases in patients' quality of life, all of which result in depressive disorders imposing a severe burden on society and making assessment of the resource-sparing potential from the medical and social perspectives important (1). Depression is recognised as a low mood with pessimistic thinking, often accompanied by a loss of interest or pleasure in normally enjoyable activities. Overall incidence of depression in North America and Europe is estimated to 16 – 17% of the population with 6% of 6-month prevalence (2).

VI.2.2 Summary of treatment benefits

The efficacy and safety of agomelatine in major depressive episodes have been confirmed in a clinical programme including 7,900 patients treated with agomelatine. Ten placebo controlled trials have been performed to investigate the short-term efficacy of agomelatine in major depressive disorder in adults. At the end of the treatment (6-8 weeks), significant efficacy was demonstrated in 6 out of 10 trials. Primary outcome was change in depression rating questionnaire for score from baseline. The maintenance of antidepressant efficacy was demonstrated in a relapse prevention trial. The incidence of relapse during the 6-months double-blind follow up period was 22% and 47% for agomelatine and placebo, respectively. Agomelatine does not alter daytime vigilance and memory in healthy volunteers.

In depressed patients, treatment with agomelatine 25 mg increased slow wave sleep without modification of REM (Rapid Eye Movement) sleep amount. Agomelatine 25 mg also induced an advance of the time of sleep onset and of minimum heart rate. From the first week of treatment, onset of sleep and the quality of sleep were significantly improved without daytime clumsiness as assessed by patients. Agomelatine also had neutral effect on heart rate and blood pressure as well as on sexual function in clinical trials.

VI.2.3 Unknowns relating to treatment benefits

There are limited or no information concerning agomelatine in children, elderly over 75 years of age, old patients with dementia, pregnant and breastfeeding women, and patients with moderate and severe kidney impairment. Therefore, it is unknown whether use of agomelatine in these populations will be profitable and safe.

VI.2.4 Summary of safety concerns

Table 12 Important identified risks

Risk	What is known	Preventability
Risk of liver toxicity (Risk of hepatotoxicity)	Increased liver enzymes (in clinical trials, increases >3 times the upper limit of the normal range were seen in 1.4% of patients on agomelatine 25 mg daily and 2.5 % on agomelatine 50 mg daily vs. 0.6% on drug with no active ingredient and will cause no effect). In less than 0.1% patients' liver impairment can occur. Liver failure was exceptionally reported with fatal outcomes.	Treatment with agomelatine should only be prescribed after careful consideration of benefit and risk in patients with liver injury risk factors e.g. obesity/ overweight/ non-alcoholic fatty liver disease, diabetes, substantial alcohol intake and in patients receiving concomitant medicinal products associated with risk of liver injury. Treatment should be initiated only after check of liver function in all patients.
Use together with strong enzyme inhibitors (Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin))	Take agomelatine together with strong inhibitors of CYP1A2 is dangerous to give. When the enzyme is stopped, the concentration in plasma increases 60 times. When agomelatine is taken together with strong/moderate CYP1A2 and CYP2C9/19 inhibitors, there is a chance of increase of plasma concentration of agomelatine.	If possible avoidance of concomitant use of medicines that inhibit CYP1A2 and CYP2C9/19 is recommended. Caution is necessary when prescribing these drugs together.

Table 13 Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Risk of considering or desiring to commit suicide. (Risk of suicidal ideation/ suicides)	Agomelatine is associated in early stages of treatment with increasing of suicidal thoughts or desiring to commit suicide. Risk is higher when agomelatine is administered to young adults (<25 years).

Table 14 Missing information

Risk	**What is known**
Limited information on use in patients with severe and moderate renal (kidney) impairment	Agomelatine itself is eliminated by urine, but no observation shows that kidney impairment will lead to problems. However, only limited clinical data on the use of agomelatine in depressed patients with severe or moderate kidney impairment with major depressive episodes is available. Therefore, caution should be exercised when prescribing agomelatine to these patients.
Use in children (paediatric) population	The safety and efficacy of agomelatine in children from 2 years onwards for treatment of major depressive episodes have not yet been established. No data are available. There is no relevant use of agomelatine in children from birth to 2 years for treatment of major depressive episodes.
Use in old patients (Use in elderly population)	The efficacy and safety of agomelatine (25 to 50 mg/day) have been established in old depressed patients (< 75years). No effect is documented in patients ≥75 years. Therefore, agomelatine should not be used by patients in this age group. No dose adjustment is required in relation to age. Agomelatine should not be used for the treatment of major depressive episodes in old patients with dementia since the safety and efficacy of agomelatine have not been established in these patients.
Use during pregnancy and breast-feeding	There is limited amount of data (less than 300 pregnancy outcomes) from the use of agomelatine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy. It is preferable to avoid the use of agomelatine during pregnancy. It is not known whether agomelatine/metabolites are excreted in human milk. Available data in animals have shown excretion of agomelatine/metabolic products in milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from agomelatine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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 special conditions and restrictions for its safe and effective use (additional risk minimisation measures).

These additional risk minimisation measures are for the following risks:

Risk of liver toxicity (Risk of hepatotoxicity)

Prescriber's guide and patient booklet
Objective and rationale: For patients and health care professionals (HCPs) to understand the risk of liver toxicity and the appropriate management of this risk to minimise its occurrence and its severity.
The Prescriber's Guide contains the following key elements: • The need to inform patients about the potential risk of transaminases elevations, the risk of liver injury and interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin); • The need to perform liver function tests in all patients before starting treatment and periodically thereafter around three, six (end of acute phase), twelve and twenty-four weeks (end of maintenance phase), and thereafter when clinically indicated; • The need to perform liver function tests at the same frequency as at treatment initiation in all patients where the dosage is increased; • Guidance in case of clinical symptoms of hepatic dysfunction; • Guidance in case of liver function test abnormality; • Caution should be exercised when therapy is administered to patients with pre-treatment elevated transaminases (> the upper limit of the normal ranges and ≤3 times the upper limit of the normal range); • Caution should be exercised when therapy is prescribed for patients with hepatic injury risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, alcohol use disorder and /or substantial alcohol intake or concomitant medicinal products associated with risk of hepatic injury; • Contraindication in patients with hepatic impairment (i.e. cirrhosis or active liver disease); • Contraindication in patients with transaminases exceeding 3 X upper limit of normal; • Contraindication in patients receiving concomitantly potent CYP1A2 inhibitors. The Patient´s Booklet contains the following key elements: • Information about the risk of hepatic reactions and clinical signs of liver problems • A guidance on the scheme of hepatic monitoring • A blood tests appointments reminder

Use together with strong enzyme inhibitors (Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)

Prescriber's guide and patient booklet
Objective and rationale: Patients and health care professionals (HCPs) to understand the risk of interaction of agomelatine with strong enzyme inhibitors and the appropriate management of this risk to minimise its occurrence and its severity.
The Prescriber's Guide contains the following key elements:

Prescriber's guide and patient booklet
• The need to inform patients about the potential risk of transaminases elevations, the risk of liver injury and interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin); • The need to perform liver function tests in all patients before starting treatment and periodically thereafter around three, six (end of acute phase), twelve and twenty-four weeks (end of maintenance phase), and thereafter when clinically indicated; • The need to perform liver function tests at the same frequency as at treatment initiation in all patients where the dosage is increased; • Guidance in case of clinical symptoms of hepatic dysfunction; • Guidance in case of liver function test abnormality; • Caution should be exercised when therapy is administered to patients with pre-treatment elevated transaminases (> the upper limit of the normal ranges and ≤3 times the upper limit of the normal range); • Caution should be exercised when therapy is prescribed for patients with hepatic injury risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, alcohol use disorder and /or substantial alcohol intake or concomitant medicinal products associated with risk of hepatic injury; • Contraindication in patients with hepatic impairment (i.e. cirrhosis or active liver disease); • Contraindication in patients with transaminases exceeding 3 X upper limit of normal; • Contraindication in patients receiving concomitantly potent CYP1A2 inhibitors. The Patient´s Booklet contains the following key elements: • Information about the risk of hepatic reactions and clinical signs of liver problems • A guidance on the scheme of hepatic monitoring • A blood tests appointments reminder

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 as this is the initial version.