VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

According to the World Health Organization, depression is a common mental disorder. Globally, more than 300 million people of all ages suffer from depression. 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.

Women typically have a double increased risk of major depression compared to men, individuals who are separated or divorced have significantly higher rates of major depression than the currently married, and occurrence of depression generally goes down with age. Depression is prevalent in patients with physical disorders, particularly in those with severe disorders such as cancer. Depression may lead to poor quality of life, more functional deficiencies, and a higher death rate.

VI.2.2 Summary of treatment benefits

Agomelatine is indicated in adults for the treatment of major depressive episodes.

Agomelatine has been compared with placebo in five short-term studies involving a total of 1,893 adults with major depression. Three of these studies included patients treated with either agomelatine or other anti-depressants (fluoxetine or paroxetine). In two studies where no active drug (comparator) was used, Agomelatin was more effective than placebo. In three other studies that included other anti-depressants, there were no differences in effectiveness. However, no effect of fluoxetine or paroxetine was seen in two of these studies, making the results difficult to interpret.

Another study comparing Agomelatin with sertraline (another anti-depressant) showed that Agomelatin was more effective than sertraline after six weeks.

Based on the available literature data, agomelatine represents an effective drug in the approved indications.

VI.2.3 Unknowns relating to treatment benefits

The safety and effectiveness of agomelatine is not fully established in use in children age less than 18 years, elderly patients (>75 years) with or without memory loss (dementia), patients with moderate or severe kidney impairment, and during pregnancy and breast-feeding.

VI.2.4 Summary of safety concerns

Table 11: Important Identified Risk(s)

Risk(s)	What is known	Preventability
Liver toxicity (Hepatotoxicity)	Agomelatine is known to be broken down (metabolised) in the liver. Cases of liver injury, including liver failure (few cases were exceptionally reported with death or liver transplantation in patients with liver risk factors), elevations of liver enzymes exceeding 10 times upper limit of normal, inflammation of liver (hepatitis) and yellowish discoloration of skin and eyes, dark-colored urine (jaundice) have been reported in patients treated with	Caution should be exercised before starting treatment and close surveillance should be performed throughout the treatment period in all patients, especially if liver injury risk factors or concomitant medicines associated with risk of liver injury are present.

Risk(s)	What is known	Preventability
	Agomelatine in the post-marketing experience. Most of them occurred during the first months of treatment. The liver damage causes elevation of liver function tests, which usually return to normal levels on cessation of Agomelatine.	Liver function tests should be periodically performed as mentioned in the label.
Allergic reactions (Hypersensitivity reactions)	Agomelatine is prohibited in patients who are allergic to the product or its excipients (inactive substance contained in the medication).	Doctors should enquire if the patient is allergic to Agomelatine. The medicine should not be taken by patients who are known to be allergic to Agomelatine.
Effect of a drug when administered with another drug (Drug interaction with potent or moderate CYP1A2 inhibitors)	Agomelatine is known to be broken down (metabolised) in the liver. Use of certain concomitant medications metabolised by certain enzymes of the liver (CYP1A2) are prohibited (e.g. fluvoxamine, ciprofloxacin etc.).	Certain medicines that are metabolised in liver should not be concomitantly used along with Agomelatine as they may result in decrease breakdown of Agomelatin and thereby increased exposure of agomelatine.
Inability to pass urine (Urinary retention)	Urinary retention has occurred rarely.	No defined measures are in place to prevent the occurrence of the event; however, agomelatine could be discontinued to prevent further worsening of urinary retention.

Table 12: Important Potential Risk(s)

Risk(s)	What is known
Skin reactions	Skin reactions are uncommonly seen (≥1/1,000 to <1/100). Rare side effects (may affect up to 1 in 1,000 people): serious skin eruption (erythematous rash), face oedema (swelling) and angioedema (swelling of the face, lips, tongue and/or throat that may cause difficulty in breathing or swallowing).
Suicidal thought (Suicidal ideation)	Thoughts of harming or killing oneself is seen uncommonly (≥1/1,000 to <1/100). These may be increased when first starting antidepressants usually about two weeks but sometimes longer. In clinical studies among children and adolescents treated with other anti-depressants, suicide-related behaviour (suicide attempt and suicidal thoughts) were more frequently observed compared to those treated with comparator placebo.
Use in patients with mental illness that causes periods of depression and elevated mood (bipolar disorders)	In clinical studies among children and adolescents treated with other anti-depressants, hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed compared to those treated with comparator placebo.

Table 13: Missing Information

Risk(s)	What is known
Use in children age less than 18 years (Use in paediatric patients [<18 years])	Agomelatine is not recommended in the treatment of depression in patients under 18 years of age since safety and effectiveness have not been established in this age group.
Use in elderly patients (>75 years) with or without memory loss (dementia)	Agomelatine should not be used for the treatment of major depressive episodes in elderly patients with dementia since the safety and effectiveness have not been established in these patients.
Use in severe or moderate kidney (renal) insufficiency (impairment)	Caution should be exercised in patients with severe or moderate renal impairment as only limited clinical data are available in these patients.
Use in pregnancy	There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of agomelatine in pregnant women. As a precautionary measure, it is preferable to avoid the use of agomelatine during pregnancy.
Use in breast-feeding (Use in Lactation)	It is not known whether agomelatine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

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 medicinal product has additional risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which will be published in EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks.

1. **Liver toxicity (Hepatotoxicity)**
2. **Effect of a drug when administered with another drug (Drug interaction with potent or moderate CYP1A2 inhibitors)**

Risk minimisation measure(s)
Objective and rationale
Agomelatine has a different mode of action and a different safety profile to existing anti-depressants. However, with the use of agomelatine, side effects on the liver has continued to be reported and an observational study has shown a considerable level of non-compliance with the recommended liver monitoring programme. The Agency has therefore concluded that there is a need to reiterate the importance of liver monitoring, in the form of education material for the HCPs and patients.

The proposed Physician's guide contains the following key messages:

- Information to HCPs regarding the potential risk of transaminases elevations, the risk of liver injury and interactions with potent CYP1A2 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;
- Contra-indication in patients with hepatic impairment (i.e. cirrhosis or active liver disease);
- Contraindication in patients with transaminases exceeding 3 × upper limit of normal;
- Contra-indication in patients receiving concomitantly potent CYP1A2 inhibitors.

The proposed Patient's Booklet contains the following key messages:

- 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

The changes in RMP over a period of time is included in the table below.

Version	Date	Safety concerns	Comments
V1.0	24 April 2017	**Important Identified Risks** 1. Hepatotoxicity 2. Hypersensitivity reactions 3. Drug interactions with potent or moderate CYP1A2 inhibitors 4. Urinary retention **Important Potential Risks** 1. Skin reactions 2. Suicidal ideation 3. Use in patients with bipolar disorders **Missing Information** 1. Use in paediatric patients(<18 years) 2. Use in elderly patients (>75 years) with or without dementia	First version of the RMP.

Version	Date	Safety concerns	Comments
		3. Use in severe or moderate renal impairment 4. Use in Pregnancy 5. Use in Lactation	
V1.1	12 January 2018	No change in the list of safety concerns	Statement that the RMP is per applicable regulations and safety concerns are aligned per the innovator is added based on CMS (RO) comments.