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.

VI.2.2 Summary of treatment benefits

For major depression, agomelatine has been studied in more than 7900 depressed patients.
Agomelatine has been compared with placebo (a dummy treatment) in ten main short-term studies involving a total of 4600 adults with major depressive episode. The main measure of effectiveness in these studies was the change in symptoms after six/eight weeks, as measured on a standard scale for depression called the Hamilton Depression Rating Scale (HAM D).
Two other main studies including 1043 patients, looked at how long it took for symptoms to return in patients who had initially responded to agomelatineduring 24 to 26 weeks of treatment.
Although the results of the studies varied, agomelatine was more effective than placebo in six of the studies. Agomelatine also was more effective than placebo to prevent the depression from returning.

Besides, six out seven efficacy studies in heterogeneous populations of depressed adult patients have shown overall an at least similar efficacy versus other antidepressants.

VI.2.3 Unknowns relating to treatment benefits

The populations where experience is limited are reflected in the Summary of Products Characteristics as follows:

- Paediatric age group (< 18 years old): Agomelatine is not recommended for use in children and adolescents.
- Elderly (≥75 years): Agomelatine should not be used by patients in this age group.
- Pregnancy: As a precautionary measure, it is preferable to avoid the use of agomelatine during pregnancy.
- Lactation: It is not known whether agomelatine/metabolites are excreted in human milk. 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.
- Hepatic impairment: Agomelatine is contra indicated and shall not be used in patients with hepatic impairment.
- Severe or moderate renal impairment: caution should be exercised when prescribing agomelatine to these patients.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Hepatotoxic reactions	Cases of liver injury, including hepatic failure (few cases were exceptionally	Yes by following the contra indications and

Risk	What is known	Preventability
	reported with fatal outcome or liver transplantation in patients with hepatic risk factors), elevations of liver enzymes exceeding 10 times upper limit of normal, hepatitis and jaundice have been reported in patients treated with agomelatine in the post-marketing setting .Most of them occurred during the first months of treatment.	recommendations on liver function monitoring
Interactions with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)	Agomelatine must not be used in patients who are taking medicines that slow down the breakdown of agomelatine in the body, such as fluvoxamine (another antidepressant) and ciprofloxacin (an antibiotic).	Yes by following the contra indication to not use agomelatinewith fluvoxamine, ciprofloxacin

Important potential risk

Risk	What is known (including reason why it is considered a potential risk)
Suicide	Depression is associated with an increased risk of thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since antidepressants all take time to work, usually about two weeks but sometimes longer. Suicidal-related events can be increased during dose changes as well.

Missing information

Risk	What is known
Limited information on use in children < 18 years old	The efficacy and safety of agomelatinehave not been studied in this population. Therefore 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 have been established in elderly depressed patients (< 75years). No effect is documented in patients ≥75 years, therefore agomelatine should not be used by patients in this age group.
Limited information on use in pregnancy women	The efficacy and safety of agomelatine have not been studied in this population. As a precautionary measure, it is preferable to avoid the use of agomelatine during pregnancy.
Limited information on use in breast-feeding women	It is not known whether agomelatine/metabolites are excreted in human milk. 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.
Limited information on use in patients with severe or moderate renal impairment	The efficacy and safety of agomelatine have not been studied in this population. 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 package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

Additional risk minimization measures (including educational material):
There are additional risk minimization measures. The educational material is included in annex 11 of the RMP and has to be submitted in case of product launch.

These additional risk minimization measures are for the following risks:

- **Hepatotoxic reactions**

Risk minimization measure: Healthcare Professional
Objective and rationale: HCPs information to manage appropriately this risk to minimize its occurrence and its severity
Main additional risk minimization measures • HCP educational materials to be provided to prescribing physicians
Risk minimization measure: Patients
Objective and rationale: To improve patient's awareness of the necessity of monitoring the liver function during treatment.
Main additional risk minimization measures • Patient's booklet to be provided to patients by doctors and/or pharmacists

- **Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)**

Risk minimization measure: Healthcare Professional
Objective and rationale: HCPs to avoid co-prescription with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)
Main additional risk minimization measures • HCP educational materials to be provided to prescribing physicians

VI.2.6 Planned post authorisation development plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
PASS using databases in four European countries category 3	To assess the incidence of hospitalisation for liver injury in current medical practice in comparison with other antidepressant drugs.	Hepatotoxic reactions	On-going	Interim report: Q3.2016 Final report: December 2017
Chart review and patients survey cross-sectional study Category 3	To evaluate - Adherence to the monitoring regimen - Compliance to relevant contraindications Information about reasons for non-compliance The PRAC recommends the submission of the protocol.	Hepatotoxic reactions	Planned	Interim report: Q4. 2017 Final report: March 2018

VI.2.7 Summary of changes to the Risk Management Plan over time

The significant changes to the RMP approved by the authorities are summarized in the below table.

Version	Date	Safety Concerns	Comment
Initial PV Plan	10.2008	1.Elevated transaminases 2.Skin reactions and suicide	1. Considered as identified risk 2. Considered as potential risks
10.2	03.2012	Elevated liver enzymes	The identified risk was renamed to include data on elevated GGT from clinical trials and post-marketing experience.
13	09.2012	Hepatotoxic reactions	The identified risk was re-qualified to include data on cases of severe hepatic dysfunction observed in clinical practice.
15	Proposed 03.2013	Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)	Proposal to consider as important identified risk, as recommended by the PRAC
		Skin reactions	Proposal to no longer consider the potential risk Skin reactions as important
		GGT increase	Proposal to no longer consider GGT increase as important
16	Proposed 11.2013	Skin reactions	To keep skin reactions as important potential risk until the prospective observational study CLE-20098-068 is finalised (final study report due in 2015)
17	Proposed 04.2014	Heppatotoxic reactions Additional PV activities :	-CPRD study replaced by PASS using databases in four European countries -Final report of the cohort study in Q4 2015 -Final report of pharmacogenomics study on Q4 2016. -Prescription survey fulfilled
18	Proposed 09.2014	Hepatotoxic reactions Effectiveness of risk minimization measures	Updated physician's guide Patient's booklet Chart review and patients survey cross-sectional study
19	Proposed 01.2016	Skin reactions	Further to cohort study results, PRAC considered that routine monitoring is sufficient and that skin reactions can be deleted as a potential safety concern in the RMP
20	Proposed 05.2016	Chart review and patients survey cross-sectional study	Revised study timelines
21	Proposed 03.2017	Chart review and patients survey cross-sectional study	Revised study timelines interim report

Version	Date	Safety Concerns	Comment
22	Proposed 06.2017		Update with data from PBRER 10 (period 20/02/2016 to 19/02/2017) and inclusion of the DCP procedure (DE/H/5306/001/DC)