12.5 Part VI.2 Elements for a Public Summary

12.5.1 Part VI.2.1 Overview of disease epidemiology

Agomelatine is indicated to treat depression in adults. Depression is a continuing disorder of mood that affects everyday life. The symptoms of depression include deep sadness, feelings of worthlessness, loss of interest, sleep disorders, feelings of anxiety and changes in weight. The expected benefits of Agomelatine are to reduce and gradually remove the symptoms related to depression [Valdoxan, 2016].

Major depression disorder (MDD) affects eating, sleeping and other everyday activities together with professional and family life. Patients affected by MDD can be at risk of self-harm. The occurrence of depression in most countries varies between 8-12%. It is estimated that in the United States approximately 3.4% of people affected by MDD commit suicide. The most common age of onset is in the early to mid-twenties. Some studies have found that MDD is more common in women than men and also in groups with lower socioeconomic status [Andrade, 2003].

12.5.2 Part VI.2.2 Summary of treatment benefits

The effectiveness of Agomelatine for the treatment of depression has been tested in several clinical trials. Agomelatine has been compared with placebo (a dummy treatment) in five main studies which involved 1,893 adults with major depression. Three of these studies included some patients treated with active comparators (other medicines used to treat depression). The main measure of effectiveness was the change in symptoms after six weeks. This was measured on a standard scale for depression called the Hamilton Depression Rating Scale (HAM-D). In the two studies where no active comparator was used, Agomelatine was found to be more effective than placebo. In the other three studies, which did include an active comparator, there were no differences in scores between the patients taking Agomelatine and those taking placebo. However, there was no effect seen with the active comparators which make the results difficult to interpret [EPAR Valdoxan, 2016].

12.5.3 Part VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorization efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment. According to the SmPC, there is limited information regarding use in children, pregnant women, breastfeeding women, the elderly (>75 years) and patients with moderate or severe kidney impairment.

12.5.4 Part VI.2.4 Summary of safety concerns

Table 12-3 Important identified risks

Risk	What is known	Preventability
Liver problems (Hepatotoxic reactions)	Some patients may get increased levels of liver enzymes in their blood during treatment with Agomelatine. Signs and symptoms of liver problems include unusual darkening of the urine, light colored stools, yellow skin/eyes, pain in the upper right belly, unusual fatigue (especially associated with other symptoms listed above).	Your doctor should have checked that your liver is working properly before starting the treatment. Follow-up tests should take place regularly. Based on the evaluation of these tests your doctor will decide whether you should receive or continue using Agomelatine. Be vigilant about signs and symptoms that your liver may not be working properly. If you observe any of these signs and symptoms of liver problems, seek urgent advice from a doctor who may advise you to stop taking Agomelatine. Special recommendations are in place to reduce the risk of liver problems.
Use with medicines which modify Agomelatine dose in the blood (Interactions with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin))	Fluvoxamine (another medicine used in the treatment of depression) and ciprofloxacin (an antibiotic) can modify the expected dose of Agomelatine in your blood.	These medicines should never be taken at the same time.

Table 12-4 Important potential risks

Risk	What is known
Suicide	If you are depressed you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer. You may be more likely to think like this: • if you have previously had thoughts about killing or harming yourself • if you are a young adult. Information from clinical trials has shown an increased risk of suicidal behavior in young adults (aged less than 25 years) with psychiatric conditions, who were being treated with an antidepressant.

Risk	What is known
	If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

Table 12-5 Missing information

Risk	What is known
Children and adolescents (Use in pediatric population, <18 years)	The safety and effectiveness of Agomelatine in this age group have not been established yet.
Use in elderly (> 75 years)	The safety and effectiveness of Agomelatine in this age group have not been established yet.
Use during pregnancy	There are no or limited amount of data from the use of Agomelatine in pregnant women. Animal studies do not indicate direct or indirect harmful effects. As a precautionary measure, it is preferable to avoid the use of Agomelatine during pregnancy.
Use during breastfeeding (Use during lactation)	It is not known whether Agomelatine is excreted in breast milk. A risk to newborns/infants cannot be excluded.
Use in patients with kidney impairment (Use in patients with severe or moderate renal impairment)	If you have trouble with your kidneys, your doctor will make an individual evaluation of whether it is safe for you to take Agomelatine.

12.5.5 Part VI.2.5 Summary of risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals (HCPs) with details on how to use the medicine, the risks and recommendations for minimizing 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 minimization measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures).

These additional risk minimization measures are for the following risks:

Serious liver problems (hepatotoxic reactions)

Risk minimization 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 minimize 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 minimization measures – Physician's guide to prescribing and Patient's booklet to highlight the risk of serious liver problems and emphasize 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 minimization 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 minimization 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 and Patient's booklet to be provided to patients.

12.5.6 Part VI.2.6 Planned post authorization development plan

None

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

Not applicable (first submission)