Part VI: Summary of the risk management plan

Summary of risk management plan for Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis (Agomelatine)

This is a summary of the risk management plan (RMP) for Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis. The RMP details important risks of Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis, how these risks can be minimised, and how more information will be obtained about Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis's risks and uncertainties (missing information).

Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis should be used.

I. The medicine and what it is used for

Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis are authorised for treatment of major depressive episodes in adults (see SmPC for the full indication). It contains Agomelatine as the active substance and it is given by oral route.

Further information about the evaluation of Valdoxan / Thymanax's benefits can be found in Valdoxan®/Thymanax®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

- For Valdoxan®: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000915/human_med_001123.jsp&mid=WC0b01ac058001d124;

- For Thymanax®: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000916/human_med_001093.jsp&mid=WC0b01ac058001d124

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis, together with measures to minimise such risks and the proposed studies for learning more about Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	- Hepatotoxic reactions - Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)
Important potential risk	- None
Missing information	- Pregnancy - Lactation

II.B Summary of important risks

Important identified risk - Hepatotoxic reactions	
Evidence for linking the risk to the medicine	In clinical trials, hepatic reactions observed on Agomelatine usually consist of asymptomatic isolated transaminases elevation of liver enzymes (transaminases) in the majority of patients, detectable within the first months of treatment and reversible. In post-marketing experience, cases of liver injury, including hepatic failure (few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic injury risk factors), elevations of liver enzymes exceeding 10 times the upper limit of normal, hepatitis and jaundice have been reported in patients treated with Agomelatine.
Risk factors and risk groups	Known risk factors of hepatic injury (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).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8 and PL sections 2 and 3. Additional risk minimisation measures:

	- Physician's guide to prescribing - Patient's booklet
Important identified risk -Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)	
Evidence for linking the risk to the medicine	Agomelatine is metabolised mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9/19 (10%). Medicinal products that interact with these isoenzymes may decrease or increase the bioavailability of agomelatine. Fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor markedly inhibits the metabolism of agomelatine resulting in a 60-fold (range 12-412) increase of agomelatine exposure. Agomelatine must not be used in patients who are taking medicines that modify/increase the expected dose of agomelatine in the blood, such as fluvoxamine (another antidepressant) and ciprofloxacin (an antibiotic).
Risk factors and risk groups	Not applicable.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3 and 4.5 and PL section 2 Additional risk minimisation measure: Physician's guide to prescribing
Missing information - Pregnancy	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and PL section 2
Missing information - Lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and PL section 2

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Valdoxan®/Thymanax®.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Valdoxan®/Thymanax®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis.