Summary of the Risk Management Plan (RMP)
for Valdoxan® / Agomelatin Servier (agomélatine)

Product concerned (brand name): Valdoxan® / Agomelatin Servier

Active substance: agomélatine

Strength: 25 mg

Pharmaceutical form: film-coated tablets

Version number: 20.1

Manufacturing Authorization Holder: Servier (Suisse) S.A.

Date of final sign off: 14/09/2021

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Valdoxan is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Valdoxan in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Servier (Suisse) S.A. is fully responsible for the accuracy and correctness of the content of the published summary RMP of Valdoxan.

Summary of risk management plan for Valdoxan®/Agomelatin Servier (agomelatin)

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

Valdoxan®/Agomelatin Servier's product information and its patient information give essential information to healthcare professionals and patients on how Valdoxan®/Agomelatin Servier should be used.

I. THE MEDICINE AND WHAT IT IS USED FOR

Valdoxan®/ Agomelatin Servier is authorised for treatment of major depressive episodes in adults and generalized anxiety disorder in adults (see the product information for the full indications). Agomelatine is the active substance.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Valdoxan®/Agomelatin Servier, together with measures to minimise such risks and the proposed studies for learning more about Valdoxan®/ Agomelatin Servier '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 patient information and product information 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®/Agomelatin Servier, 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®/ Agomelatin Servier 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®/ Agomelatin Servier. 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 risks	- None
Missing information	- Pregnancy - Lactation

II.B Summary of important risks

Important identified risks: Hepatotoxic reactions	
Evidence for linking the risk to 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: product information sections: « Dosage/ Administration », « Contraindications», « Warnings and precautions», «undesirable effects» and patient information section « What precautions should be taken before you take/use Valdoxan? » and « How to use Valdoxan? » 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 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: product information section «Contraindications » and « Interactions » and patient information section « What precautions should be taken before you take/use Valdoxan? » Additional risk minimisation measure: Physician's guide to prescribing
Missing information - Pregnancy	

Risk minimisation measures	Routine risk minimisation measures: product information sections : «Pregnancy, lactation » and patient information section « What precautions should be taken before you take/use Valdoxan ? » and « How to use Valdoxan ? »
Missing information - Lactation	
Risk minimisation measures	Routine risk minimisation measures: product information sections : «Pregnancy, lactation», « What precautions should be taken before you take/use Valdoxan ? » and « How to use Valdoxan ? »

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®/Agomelatin Servier.

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

There are no studies required for Valdoxan®/ Agomelatin Servier.