EU RISK MANAGEMENT PLAN for

Valdoxan® / Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis (Agomelatine)

EU Risk Management Plan for Agomelatine

RMP version to be assessed as part of this application:

RMP Version number: 26.0

Data lock point for this RMP:31/07/2024

Date of final sign off: 25/09/2024

Rationale for submitting an updated RMP: Revision of safety concerns and additional risk minimization measures.

Summary of significant changes in this RMP:
Deletion of safety concerns (risks and missing information).
Deletion of additional risk minimization measures (aRRMs).
Update with the results from the paediatric clinical studies CL2-20098-075, CL3-20098-076 and the post-marketing data as of 31 July 2024.

Details of the currently approved RMPs:
Version number: 25.0

Approved by the PRAC during the assessment of the PSUSA/00000071/202102: the distribution paths of educational materials have been revised and there is no more active distribution of educational materials following the MAH proposal to make them available on MAH's affiliates/or Agency local websites.

Date of approval (CHMP opinion date): 30 September 2021

QPPV name: **Dr Fairouz SMAIL-AOUDIA**

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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Part I: Products Overview

Table Part I.1 – Product Overview

Active substance **(INN or common name)**	AGOMELATINE
Pharmacotherapeutic group (ATC Code)	N06AX22
Marketing Authorisation Holder	Les Laboratoires Servier (France) Servier (Ireland) Industries Ltd Biogaran Anpharm Przedsiebiorstwo Farmaceutyczne S.A. Egis Pharmaceuticals PLC
Medicinal products to which this RMP refers	VALDOXAN® Agomelatine <MAH>
Invented names in the European Economic Area (EEA)	VALDOXAN® Agomelatine Anpharm Agomelatine Biogaran Agomelatine Egis
Marketing authorisation procedure	EMEA/H/C/915 DE/H/5306/001/DC
Brief description of the product	Antidepressant, melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist
Hyperlink to the Product Information	Module 1.3.1
Indication in the EEA	Current: Treatment of major depressive episodes in adults
Dosage in the EEA	Current: The recommended dose is 25 mg once daily taken orally at bedtime. After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25mg tablets, taken together at bedtime. Decision of dose increase has to be balanced with a higher risk of transaminases elevation. Any dose increase to 50 mg should be made on an individual patient benefit/risk basis and with strict respect of LFT monitoring. Liver function tests should be performed in all patients before starting treatment. Treatment should not be initiated if transaminases exceed 3 X upper limit of normal. During treatment transaminases should be monitored: periodically after around three weeks, six weeks (end of acute phase), twelve weeks and twenty-four weeks (end of maintenance phase) and thereafter when clinically indicated. Treatment should

	be discontinued if transaminases exceed 3 X upper limit of normal. When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment. Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.
Pharmaceutical form and strength	Current: Film-coated tablet, 25 mg
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication and target population(s)

Indication

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

Major Depressive Disorder (MDD) is a common but serious condition with an average lifetime and 12-month prevalence estimates of 14.6% and 5.5% in the high-income and 11.1% and 5.9% in the low- to middle-income countries. MDD is twice as frequent in women as in men. It is also strongly linked to social condition (Bromet, 2011). Major Depressive Disorder is characterized by substantial symptomatic distress such as the all- pervasive feelings of despair, worthlessness, and guilt. The patient loses interest in his/her activities and takes no pleasure in life. Sleep and appetite are disrupted, weight may vary, and patient cannot concentrate and becomes indecisive, retarded, or agitated. These symptoms are often associated with suicidal feelings.
This symptomatic distress is accompanied by major impairment of interpersonal, social, and occupational functioning, and society carries an appreciable burden (Lépine, 2001; Greden, 2001, Bromet, 2011). This burden is high in male, but still higher in female patients (WHO, 2017). Maternal depression also appears as risk factor for poor growth in young children (Rahman, 2008). Patients may be disinclined to admit such symptoms for fear of stigmatization; thus, the diagnosis is often missed.

The incidence, prevalence, mortality, and demographic profile of the MDD population are provided in the following table.

Epidemiology of the major depressive disorders

Indication/target population	**Major depressive episodes in adults**
Incidence	Major Depressive Disorders first **incidence** of **1.72 per 100 person-years** in men and **3.90 per 100 person-years** in women have been reported in The Dutch NEMESIS survey of people aged 18-64 (Bijl, 2002).
Prevalence	The majority of European surveys of MDD (defined by DSM-IV, DSM III or ICD-10) have reported prevalence rates in the general population ranging from **2 % to 8 % for a year** (Paykel, 2005) and of 16 % for a lifetime. It approximately corresponds to 322 million people worldwide (WHO, 2017).
Demographics of the target population	Prevalence rate vary by age, peaking in older adulthood (WHO, 2017). Women are at greater risk than men (2 females / 1 male), as well as separated or divorced persons, and persons with lower socioeconomic status (Blazer,2000; Freeman,2016).

Indication/target population	**Major depressive episodes in adults**
Risks factors for the disease	As the cause of depression remains unknown, several risk factors have been found to be associated with a greater incidence of the disease and especially: - Gender (women) - Family (mainly first-degree relatives) history of mood disorders and/or alcohol abuse or dependence, - Early childhood trauma: loss of a parent or parental divorce before adolescence, child neglect, physical, emotional, or sexual abuse, - Other psychiatric illness (especially alcohol/substance abuse or dependence, anxiety disorders, sleep disorders, schizophrenia, dementia at early stages), - Stress, tobacco quitting, - Stressful life events such as bereavement, affective trauma, unemployment, - Susceptibility in specific genes (e.g. CREB1 in chromosome 2) Severe somatic illness (e.g. cancer, cardio-vascular diseases, chronic viralinfections), thyroid disorder, hormonal imbalances, - Medications (e.g. sedatives, pain medications), psychoactive drugs - Obsessive-compulsive, histrionic and borderline personality Disorders - Mode of life: marital status (divorced, separated, living alone), urban mode of living, poor socio-economic status
Main treatment options	Antidepressants
Mortality and morbidity	**Mortality by suicide** is 30 times higher in a depressed population than in a non-depressed one. MDD is also associated with a higher rate of all-**cause mortality** relative to that observed in the general population and it is estimated that the disorder reduces the lifespan of sufferers by an average of approximately 10 years (Montgomery, 2006). While the overall rate of death by **suicide** in persons suffering from depressive disorders is around 15%, the suicide rate may reach 40% in depressed patients also experiencing severe anxiety disorders, panic attacks or obsessive-compulsive disorders (Ballenger, 1999).
Important co-morbidities found in the target population	Co-morbidities are common in patients with MDD. The most frequent important co-morbidities in the MDD population are other mental disorders and insomnia. It has been shown that 72 % of the respondents with lifetime MDD also meet the criteria for at least one other mental disorder (US National Co morbidity Survey conducted in 2001-2002), including: - Anxiety disorder in 59 %; - Substance use disorders (include alcohol or drug abuse or dependence) in 24 %; - Impulse control disorder in 30 % (Kessler, 2003). MDD is also frequently associated with a variety of somatic complaints, resulting in a high frequency of medical consultations for conditions other than depression (Wells, 1989; US Public Health Service, 2006). As an example, insomnia is reported by 70 % to 90 % of depressed / psychiatric patients (Philip, 2006). Up to 20 % of survivors of acute myocardial infarction meet diagnostic criteria for major depression and this co-morbidity carries a more than five-fold increased risk of cardiac mortality within six months (Jiang, 2005). Depression has also been reported to increase the risk of functional decline and death in patients with heart failure (Vaccarino, 2001) and the risk of stroke mortality (Everson, 1998). Post-stroke depression reported prevalence estimates range from 10 % to 64 % (Aben, 2001).

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

- Key issues identified from acute or repeat-dose toxicity studies:
  - single-dose toxicity studies indicated a low acute toxicity, with dose-related sedative effects.
  - repeated dose toxicity studies in rodents and monkeys showed liver findings associated with liver enzyme inductions (increased liver weight with or without hepatocellular hypertrophy). No hepatotoxicity signal assumed to be clinically relevant was observed.
- Reproductive/developmental toxicity: Reproduction studies in the rat and the rabbit showed no effect of agomelatine on fertility, embryofoetal development and pre- and post-natal development.
- Genotoxicity: A full battery of genotoxicity tests including in vitro and in vivo tests has shown that agomelatine is not genotoxic.
- Carcinogenicity: In carcinogenicity studies agomelatine has been shown to increase the frequency of liver tumors in male rats and male and female mice at liver enzyme inducing doses (from 125 and 500 mg/kg p.o. in the diet respectively) without modifying tumor latency and survival in comparison to control animals. These effects are similar to those seen with the classical non genotoxic rodent hepatic enzyme inducer phenobarbital.

In the rat study, a slight increase in benign mammary tumors (fibroadenomas) was observed at the top-dose but was considered to be due to expected biological variation.
DNA adducts were detected following four weeks *in vivo* agomelatine administration in rat but not in studies *in vitro* where similar pattern of metabolites would have been produced. The failure to unequivocally demonstrate covalent binding of radiolabelled agomelatine to DNA is in agreement with the negative results in conventional genotoxicity tests. Positive 32P-postlabeling parallels liver enzyme induction as an indirect cell-mediated effect. This was shown in a study in rats after single and 28-day repeated administration.
The lack of genotoxic potential in an extensive battery of *in vitro* and *in vivo* tests in conjunction with the results of the investigative studies allow to conclude that agomelatine enhances liver tumors through non-genotoxic mechanisms and does not pose a carcinogenic hazard to humans at the non-enzyme inducing therapeutic doses of 0.4 mg to 0.8 mg/kg.

In view of these data, it can be concluded that the agomelatine toxicity program indicates that recommended doses of agomelatine should prove to be safe in humans.

Safety pharmacology

General safety pharmacology testing of agomelatine has shown few effects other than sedation and related changes at high doses.

- Single high doses of agomelatine have no effect on haemodynamic parameters in the rat and in the monkey. *In vitro*, agomelatine does not increase action potential duration in Purkinje fibres and does not inhibit significantly the recombinant HERG) current in transfected COS-7 cells.
- Minor effects on the hypothalamo-hypophyseal axis or the plasma levels of sex hormones in the male and female rat were observed. At a high dose (3600ppm in the diet), agomelatine has some minor effects, predominantly inhibitory on pituitary adrenal and gonadal hormones.
- Agomelatine has no effect on gastro-intestinal and renal parameters in the rat.

- The drug demonstrated no abuse potential in a number of standard tests.

Findings from reproductive studies

Findings from reproductive studies	Relevance to human usage
No effect on: - fertility (rat), - embryo foetal development (rat, rabbit), - peri-postnatal development (rat)	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.
Agomelatine or its metabolites are excreted in the milk of lactating rats.	It is not known whether agomelatine/ metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of agomelatine/metabolites in milk. A risk to the newborns/infants cannot be excluded. 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. Statements regarding the use of agomelatine in pregnant and lactating women have been included in section 4.6 of the SmPC.

SII Conclusions on non-clinical data

No safety concern has been identified in non-clinical studies performed with agomelatine.

Part II: Module SIII - Clinical trial exposure

- **PKH and Phase I studies**

More than 1000 healthy or patient volunteers (not included in the overall safety set) were investigated in pharmacology studies.

- **Phase II and Phase III studies**

The Integrated Analysis of Safety was performed on data from 54 completed studies for adults and two studies for children and adolescents.

The largest safety set, Overall safety set (OSS), includes data from all Phase II and Phase III studies of patients with MDD or with one of the different diseases studied in the agomelatine development program (e.g. elderly patients with primary insomnia or with Alzheimer's disease, patients with delayed sleep phase syndrome, patients with schizophrenia, generalized anxiety disorder…).

The OSS adult set consist of 10591 patients who received agomelatine (9506 patients received agomelatine 25/50 mg), 2026 received placebo and 3392 received an active control (fluoxetine, paroxetine, venlafaxine, escitalopram, sertraline, or duloxetine).

The MDE adult set (MDE) comprises a total of 8532 patients who were exposed to agomelatine over the course of 37 completed clinical MDE studies (35 MDD and 2 bipolar studies), including long- term treatment of 52 weeks or more with agomelatine, equivalent to 41127.2 patient-months of exposure. The patient-months of agomelatine exposure is 8.9 fold higher than placebo (4611.3

patient-months), and 3.8 fold higher than the active control (10926.1 patient-months). Among the 8532 MDE patients exposed to agomelatine, 8084 patients were treated at therapeutic doses 25/50 mg. Among these patients, 2356 had 6-month of exposure to agomelatine, and 1094 had 1-year of exposure to agomelatine.

The MDE all set comprises 8948 patients who were exposed to agomelatine, including the paediatric population. 306 patients received agomelatine 10 mg, 5904 patients received agomelatine 25 mg and 2422 patients received agomelatine 50 mg.

Concerning the paediatric population, 163 patients were male, and 253 patients were female. Out of these 416 patients, 174 received agomelatine 10 mg and 242 received agomelatine 25 mg. Among these patients, 317 had 3 months exposure to agomelatine, 288 had a 6-months exposure to agomelatine and 240 had 1-year exposure to agomelatine.

Exposure in terms of persons and person-months by duration, dose, age group and gender for agomelatine-treated patients in the overall safety set, in the MDE set (adult and all), and exposure in terms of persons and person-months in special populations are provided in the following table:

Safety sets - Exposure to agomelatine by duration, dose, age group, gender and in special populations

	OSS all N=11 007 (54821.9 PM)		**MDE all N=8948** (46905.7 PM)		**OSS adult N= 10591** (49043.5 PM)		**MDE adult N= 8532** (41127.2 PM)		**MDE pediatric N=416** (5778.42 PM)	
	n	**PM**	**n**	**PM**	**n**	**PM**	**n**	**PM**	**n**	**PM**
Duration										
Cumulative up to 1 month	9756	17.79	7980	17.01	9403	19.17	7627	18.54	353	6.11
Cumulative up to 3 months	6071	11.01	5109	10.89	5754	11.73	4792	11.65	317	5.49
Cumulative up to 6 months*	2801	5.11	2449	5.22	2513	5.12	2161	5.25	288	5.0
Cumulative up to 12 months**	1404	2.56	1334	2.84	1164	2.37	1094	2.66	240	4.15
Dose of exposure										
1-5 mg	547	858.1	302	488.04	547	858.1	302	488.0	-	-
10 mg	643	4362.9	306	3105.85	469	1775.9	132	518.9	174	2587.0
25 mg	6832	32863.9	5904	28807.46	6590	29672.4	5662	25616.0	242	3191.5
50 mg	2916	16670.8	2422	14490.6	2916	16670.8	2422	14490.6	-	-
100 mg	69	66.2	14	13.7	69	66.2	14	13.7	-	-
Age group (years)										
<12	96	1220.8	96	1220.8	-	-	-	-	96	1220.8
[12-18[	320	4558.8	320	4557.7	-	-	-	-	320	4557.7
[18-65 [	9521	44735.9	8018	38770.8	9521	44735.9	8018	38770.8	-	-
[65-75 [	674	2806.1	410	1959.2	674	2806.1	410	1959.2	-	-
[75-85 [	296	1043.3	100	384.5	296	1043.3	100	384.5	-	-
≥ 85	99	457.0	4	12.7	99	457.0	4	12.7	-	-
Gender										
Male	3503	17403.9	2757	14686.7	3340	15184.0	2594	12466.8	163	2219.9
Female	7504	37418.0	6191	32218.9	7251	33859.5	5938	28660.4	253	3558.5
Special populations										
Renal impairment										
<50 mL/min	272	1075.4	58	226.4	272	1075.4	58	226.4	-	-
[50-80] mL/min	2619	11294.3	1971	8905.8	2619	11294.3	1971	8905.8	-	-
> 80 mL/min	5705	24257.5	4535	19638.4	5705	24257.5	4535	19638.4	-	-
missing	1995	12416.3	1968	12356.6	1995	12416.3	1968	12356.6	-	-
Hepatic impairment	Not included in clinical studies									

Pregnant women#	19	0.20	17	0.21	19	0.20	17	0.21	-	-
Lactating women	Not included in clinical studies									
Relevant comorbidities										
Obesity (BMI ≥ 30 kg/m²)	2192	11722.2	1923	10590.4	2192	11722.2	1923	10590.4	-	-
Alcohol consumers	3208	14847.3	2440	11719.3	3208	14847.3	2440	11719.3	-	-
Smokers	2222	9821.9	1861	8342.6	2222	9821.9	1861	8342.6	-	-

** Exposed at least 175 days*
*** Exposed at least 350 days*
 # under agomelatine treatment or within 1 month after the end of agomelatine treatment in clinical studies
CrCl creatinine clearance
Number of patients (N) and corresponding Number of Patients-Months (PM)
*PM Incidence expressed per 100 Patients-Months (n/PT)*100*

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

These exclusion criteria did not reduce the representativeness of the studied population towards the target one and are described in the table hereafter.

Criterion	**Reason for exclusion**	**Is it considered to be included as missing information? Yes/No**	**Rationale:** ***(if not included as missing information)***
Females with childbearing potential without reliable means of contraception	To avoid pregnancy during the clinical trial	No	Precautionary safety measure due to lack of data in human pregnancy
Pregnancy	Precautionary safety measure due to lack of data in human pregnancy	No	Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. No safety concern arose from the use of Agomelatine in pregnant women from post-marketing experience, suggesting that a different safety profile is not expected from Agomelatine use in this population. However, patients should avoid the use of Valdoxan during pregnancy.

Criterion	**Reason for exclusion**	**Is it considered to be included as missing information? Yes/No**	**Rationale:** ***(if not included as missing information)***
Lactation	Precautionary safety measure due to lack of data in human lactation	No	It is not known whether agomelatine/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of agomelatine/metabolites in milk. A risk to the newborns/infants cannot be excluded. No safety concern arose from the use of Agomelatine in breastfeeding women from post-marketing experience, suggesting that a different safety profile is not expected from Agomelatine use in this population. However, patients should discontinue breast-feeding or discontinue/abstain from Valdoxan therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Paediatric population (< 7 years)	Not targeted population	No	This population is not considered as a target population.
Patients with severe or moderate renal impairment	Potential safety concerns related to Agomelatine elimination	No	No relevant modification in agomelatine pharmacokinetic parameters in patients with severe renal impairment has been observed. No safety concern arose from the use of Agomelatine in patients with renal impairment from post-marketing experience, suggesting that a different safety profile is not expected from Agomelatine

Criterion	**Reason for exclusion**	**Is it considered to be included as missing information? Yes/No**	**Rationale:** ***(if not included as missing information)***
			use in this population. However, caution should be exercised when prescribing agomelatine to these patients.
Patients with hepatic impairment	Safety concerns related to Agomelatine metabolization (mainly by the liver)	No	Contra-indication in the section 4.3 of the SmPC
Other depression than Major Depressive Episode (MDE)	Not targeted indication	No	Not included in the registered indication
Resistant depression	Not targeted indication	No	Not included in the registered indication
Marked suicidal intent	Ethical consideration to avoid exposure to a placebo	No	Close supervision of patients at high suicidal risk is recommended in section 4.4 of the SmPC
Acute or chronic psychosis	Targeted population in the patients with the MDE Indication	No	Not included in the registered indication
Psychotropic treatments (antidepressants , antipsychotics, barbiturates, lithium salts, antiepileptics, benzodiazepines , hypnotic treatments)	To avoid bias in the assessment of the efficacy	No	No drug interaction detected in specific drug-drug interaction studies (see information in the section 4.5 of the SmPC), except for Fluvoxamine (see information in the section 4.3 of the SmPC)
Treatment with thyroid hormones started within the 3 months prior to inclusion	To avoid inclusion of patients with depressive symptoms due to unstable thyroid function and bias in the assessment of the efficacy	No	Patients treated for more than 3 months were included in clinical trials with no specifics warning

Criterion	**Reason for exclusion**	**Is it considered to be included as missing information? Yes/No**	**Rationale:** ***(if not included as missing information)***
Treatment acting on central nervous system (corticosteroids, ACTH, ...), exogenous melatonin	To avoid bias in the assessment of the efficacy	No	No drug interaction detected in specific drug-drug interaction studies (see information in the section 4.5 of the SmPC), except for Fluvoxamine (see information in the section 4.3 of the SmPC)

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program See table Safety sets - Exposure
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities: • Patients with hepatic impairment	Not included in the clinical development program
• Patients with renal impairment	Not included in the clinical development program However, in the MDE set, 58 agomelatine treated patients (56 on agomelatine 25/50 mg) met the criterion for moderate renal impairment (CrCl < 50 mL/min/1.73 m^2) and 1971 agomelatine treated patients (1825 on agomelatine 25/50mg) the criterion for mild renal impairment (50<CrCl < 80 mL/min/1.73 m^2). See table Safety sets - Exposure
Population with relevant different ethnic origin	Not available. Ethnic origin was not collected in clinical trials.

Subpopulations carrying relevant genetic polymorphisms	Not available. No genetic polymorphisms were assessed during development program.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The usual administration schedule of Agomelatine is 25 mg once daily.
The estimated post-authorisation exposure is based on the sales volumes, the defined daily dose of 25 mg daily and months of 30.4 days.

SV.1.2 Exposure

From initial MA (19 February 2009) until 31 July 2024, cumulative patient exposure to Agomelatine is estimated to be 4 793 782 Patient-Years (PY), i.e. 2 539 568 PY from EU countries and 2 254 215 PY from non-EU countries, as presented in the table below.

Cumulative patient exposure from marketed experience for Agomelatine

	Number of Patient-Years
Countries	**Since Market Authorisation through 31 July 2024**
EU countries	**2 539 568**
Non-EU countries	**2 254 215**
All countries	**4 793 782**

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Early studies have shown that Agomelatine has only an affinity for melatonergic and 5-HT2C receptors.
No evidence of drug addiction potential has been shown in animals nor in specific Phase I clinical studies using Visual Analogue Scales and specific questionnaires (ARCI 49). In phase II and phase III trials, there were no cases of drug abuse or drug seeking behaviour in the patients.
In one specific study (CL3-030) designed to assess discontinuation symptoms by the Discontinuation Emergent Signs and Symptoms (DESS) checklist in patients with remitted depression, no discontinuation syndrome were observed after Agomelatine abrupt treatment cessation.

Over the 15-year period of post-marketing surveillance, a total of 31cases of Agomelatine abuse/misuse were reported**.** Considering their low reporting rate as well as the nature of the reported reactions, no new signals were evidenced.

In view of these data the potential for misuse for illegal purposes is considered as low.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The safety concerns identified in the initial RMP submission were:

- Identified risk: Elevated transaminases.

  During the initial evaluation the CHMP considered that "Overall the safety profile of agomelatine did not pose particular concerns; increases in liver enzyme values could have been addressed by a risk management plan". Therefore, elevated transaminases have been considered as the only clinical risk to be addressed in the initial RMP. Detailed information on frequency, reversibility, severity, background incidence/prevalence, risk factors, potential mechanisms, preventability, potential public health impact and regulatory action taken regarding elevated transaminases were provided.

- Potential risks: Skin reactions, Suicide.

  Skin reactions: In the MDD database, the incidences of skin emergent adverse events (EAEs) in agomelatine and placebo groups in patient-months were similar (5.7%, 1.17 per 100 patient-months versus 3.8%, 1.25 per 100 patient-months). However, following the CHMP request, skin reactions has been added as potential risk. Detailed information on frequency, severity, background incidence/prevalence, risk factors, potential mechanisms, preventability, potential public health impact and regulatory action taken regarding skin reactions were provided.

  Suicide: In agomelatine phase III trials, no increased risk of suicidality in patients treated with agomelatine (including in patients aged 18-30 years) has been observed. However, as for other antidepressants, a statement regarding suicidality has been included in Section 4.4 of the SmPC. Moreover, suicides and related events will be closely followed as a potential risk. Detailed information on frequency, severity, background incidence/prevalence, risk factors, potential mechanisms, preventability, potential public health impact and regulatory action taken regarding suicide were provided.

- Missing information: Paediatric age group (<18 years), Elderly (> 75 years), Pregnancy, Lactation, Severe or moderate renal impairment and Hepatic impairment. These conditions were not studied in clinical trials, and at the time of the initial RMP there were not enough knowledge of the safety profile of Agomelatine use in these specific populations.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The following safety concerns have been removed in the updated RMP:

- Hepatotoxic reactions and Interactions with potent CYP1A2 inhibitors previously classified as important identified risks were removed ;
- Missing information: Pregnancy and lactation were removed.

Hepatotoxic reactions were an important identified risk in the RMP. These reactions have been characterized through the 15 years post-marketing, and no new information has been obtained. In addition, the incidence of hepatotoxic reactions has steadily decreased during the last years. Based on these data, the PRAC considered that hepatotoxic reactions should not be an important identified risk in the RMP any longer. However, hepatotoxic reactions are still considered as an important identified risk for agomelatine and characterised as such in the PSURs.

Interactions with potent CYP1A2 inhibitors were an important identified risk in the RMP. These interactions have been characterized through the 15 years post-marketing, and no new information has been obtained. In addition, the incidence of interactions has steadily decreased during the last years. Based on these data, the PRAC considered that interactions with potent CYP1A2 inhibitors should not be an important identified risk in the RMP and PSUR any longer and that routine surveillance is sufficient in the future.

Pregnancy and lactation were considered as missing information in the RMP. These conditions have been characterized through the 15 years post-marketing, and no new information has been obtained. Based on these data, the PRAC considered that pregnancy and lactation can be removed as missing information in the RMP, and that routine surveillance is sufficient in the future. However, pregnancy and lactation will continue to be characterized as missing information in the PSUR.

The following updates in safety concerns have been made in previous RMP versions:

In RMP version 13 (dated 18 September 2012): the important identified risk elevated liver enzymes was requalified as hepatotoxic reactions in order to include data on cases of severe hepatic dysfunction observed in clinical practice. This review was performed in the procedure EMEA/H/C/915/R/017. Of note, the initial identified important risk elevated transaminases had been renamed as elevated liver enzymes in RMP version 9(dated 23 September 2011).

In RMP version 15 (dated 25 March 2013): Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) was considered as a new important identified risk, as recommended by the PRAC. This review was performed in the procedure EMEA/H/C/915/R/017.

In RMP version 18 (dated 24 September 2014): Hepatic impairment, previous classified as missing information, is no longer considered as such. As hepatotoxicity is an important identified risk, hepatic impairment is a contraindication for the product, and detailed recommendations for monitoring of hepatic function is already included in the SmPC and PIL. This review was performed in the procedure EMEA/H/C/915/PSUV/23.

In RMP version 19 (dated 20 January 2016): Skin reactions previously classified as important potential risks was removed following the cohort study results (CLE-20098-068). This review was performed in the procedure EMEA/H/C/000915/II/0030.

In RMP version 24 (dated 22 October 2020): Suicide events previously classified as important potential risks were removed, as well as the following Missing information: paediatric age group (< 18 years old), elderly (≥ 75 years) and severe or moderate renal impairment are removed. Suicide events are considered as important potential risks and characterized as such in the PBRER. Use in paediatric age group (< 18 years old), elderly (≥ 75 years) and severe or moderate renal impairment are considered as missing information and characterized as such in the PBRER. These safety concerns are managed through routine Pharmacovigilance activities. This review was performed in the procedure EMEA/H/C/xxxx/WS/1849.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: None.

SVII.3.2. Presentation of the missing information

Missing information: None.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Important identified risks	None
Important potential risk	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The safety profile of agomelatine is well characterised.
Therefore, routine pharmacovigilance activities (including signal detection) are sufficient. The monitoring of the reported occurrence of adverse reactions in the post marketing setting is performed through the signal detection process, on a 6 monthly basis, using qualitative and quantitative analysis.

Regarding Hepatotoxic reactions, routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are described hereafter:

Specific adverse reaction follow-up questionnaires for hepatotoxic reactions:

- Documentation of Liver adverse reactions including abnormal liver function tests from all sources is retrieved through of a Hepatic Disorders Questionnaire (see Annex 4) including:
  - Presence of concomitant potential hepatotoxic drugs,
  - Medical history or context that may predispose for hepatic adverse events,
  - Information to document whether treatment recommendations in the SmPC concerning increased liver transaminases have been followed.

Other forms of routine pharmacovigilance activities for hepatotoxic reactions:

- Submission of cumulative re-estimated data on ALT and/or AST, ALP value >3 ULN and total bilirubin > 2 ULN from the updated overall safety data base in the framework of the PBRERs.
- Liver adverse reactions including abnormal liver function tests from all sources are collected and specifically reviewed in the framework of the PBRERs
- Safety information on GGTs increase whatever the source of information (clinical studies, spontaneous report …) are routinely collected and specifically reviewed in the framework of the PBRERs.

III.2 Additional pharmacovigilance activities

Not applicable

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures: None.

V.2. Additional Risk Minimisation Measures: Educational materials (Physician's guide to prescribing and Patient's booklet) concerning Hepatotoxic reactions and Interactions with potent CYP1A2 inhibitors were removed in the updated RMP as recommended by the PRAC and endorsed by the MAH. It was considered that both safety concerns are now well-known among physicians. Precautions to take to avoid hepatotoxicity (contraindications to use, warnings and liver function monitoring) are adequately described in the SmPC and PL. Information on these issues is also implemented in clinical guidelines in many countries and can thus, be regarded as implemented in clinical practice. The contraindication to potent CYP1A2-inhibitors is also stated in the SmPC and PL, and cases reported in a context of contraindication have been few the last years (declining incidence).

V.3 Summary of risk minimisation measures: Not applicable.

Part VI: Summary of the risk management plan

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

This is a summary of the risk management plan (RMP) for Valdoxan®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis.

Valdoxan®/ 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®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis should be used.

This summary of RMP for Valdoxan®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment (EPAR).

Important new concerns or changes to the current ones will be included in updates of Valdoxan®/ Agomelatine Anpharm / Agomelatine Biogaran / Agomelatine Egis' RMP.

I. The medicine and what it is used for

Valdoxan®/ 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 benefits can be found in Valdoxan®/'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;

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

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 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®/ 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®/ 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	- None
Important potential risk	- None
Missing information	- None

II.B Summary of important risks

Not applicable.

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®

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

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

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Follow-up forms: Hepatic Disorders Questionnaire

HEPATIC ADVERSE EVENTS - AGOMELATINE

PATIENT INFORMATION

Gender: ..... Age: ..... year-old Weight: ..... kg Height: ..... cm BMI: .....

AGOMELATINE INFORMATION

Daily dosage: ..... Indication: .....
Date of FIRST intake: ...../...../.....
Daily dosage increase ☐ Yes ☐ No ☐ Unknown Date: ...../...../.....
Date of LAST intake: ...../...../.....
Hepatic lab tests:
- Before the introduction of VALDOXAN ☐ Yes ☐ No ☐ Unknown
- At daily dosage increase ☐ Yes ☐ No ☐ Unknown ☐ NA

EVENT INFORMATION

Verbatim: ..... Onset date: ...../...../.....
Agomelatine withdrawal ☐ Yes ☐ No ☐ Unknown
Follow-up of the event
Hepatic lab tests : ☐ Yes ☐ No ☐ Unknown
Frequency of hepatic lab tests: .....
Outcome
☐ Recovered ☐ Recovering ☐ Not Recovered ☐ Unknown

(ATTACH REPORTS)	BASELINE YES NO UNK	3 WEEKS YES NO UNK	6 WEEKS YES NO UNK	12 WEEKS YES NO UNK	24 WEEKS YES NO UNK	OTHER YES NO UNK
ASPARTATE AMINOTRANSFERASE	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
ALANINE AMINOTRANSFERASE	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐

CLINICAL FINDINGS	YES	NO	UNK
Symptoms	☐	☐	☐
If YES, details:			
.....			
.....			

LAB TESTS *(ATTACH REPORTS)*	YES	NO	UNK
Other hepatic lab tests (Bilirubin, ALP, GGT)	☐	☐	☐
Prothrombin Time or INR	☐	☐	☐
Factor V	☐	☐	☐
Viral serology (HAV, HBV, HCV, HEV, EBV, CMV)	☐	☐	☐
Autoimmune investigations	☐	☐	☐

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MEDICAL CONTEXT/HISTORY (SPECIFY)	YES	NO	UNK
Obesity	☐	☐	☐
Acute / Chronic alcohol intake	☐	☐	☐
Diabetes	☐	☐	☐
Dyslipidemia	☐	☐	☐
Hypotension (haemorrhage…)	☐	☐	☐
Heart failure	☐	☐	☐
Non-alcoholic fatty liver disease	☐	☐	☐

IMAGING FINDINGS (ATTACH REPORTS)	YES	NO	UNK
Abdominal ultrasound scan	☐	☐	☐
Abdominal CT scan	☐	☐	☐
Liver biopsy	☐	☐	☐

TOXIC EXPOSURE / CONCOMITANT TREATMENTS	YES	NO	UNK
Alcohol ..... g/day	☐	☐	☐
Mushrooms intake	☐	☐	☐
Paracetamol	☐	☐	☐
NSAIDs	☐	☐	☐
Antibiotics	☐	☐	☐
Antiepileptic drugs	☐	☐	☐
Statins	☐	☐	☐
Other	☐	☐	☐
Specify:			

FOR ANY LAB TEST, PLEASE COLLECT EXACT DATE OF LAB TEST, EXACT VALUE, UNIT AND REFERENCE RANGE.

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Annex 6 - Details of proposed additional risk minimisation activities

Not applicable.