19 September 2013
EMA/702809/2013
Pharmacovigilance Risk Assessment Committee (PRAC)

Valdoxan/Thymanax

(agomelatine)

Procedure No. EMEA/H/C/000915/PSUV/0017 (Valdoxan)

Marketing authorisation holder: Les Laboratoires Servier

Procedure No. EMEA/H/C/000916/PSUV/0019 (Thymanax)

Marketing authorisation holder: Servier (Ireland) Industries Ltd

Assessment report for a variation including a contraindication

Assessment report as adopted by the CHMP with all commercially confidential information deleted

Following the PRAC recommendation on this PSUR, the Committee for Medicinal Products for Human Use (CHMP) adopted an opinion. This opinion's annex IV "Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisations" and any appendix can be found under the Assessment history tab of the EPAR.

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1. PSUR Data

1.1. Introduction

Agomelatine is a new antidepressant with a distinct neurochemical profile. It is a melatonin receptor agonist (MT1 and MT2) and a subtype 5-HT2C serotonin receptor antagonist. The indication is major depressive episodes in adults.

The data presented is the 6th PSUR for Valdoxan covering the period 20022012 – 19022013.

As part of the procedure, the MAH proposed to update the product information as follows:

- Include "restless leg syndrome" as an ADR in section 4.8 of the SmPC and update the package leaflet accordingly.

1.2. Worldwide marketing authorisation status

Agomelatine was first authorised in Ukraine on 28.08.2006 and in the EU on 19.02.2009 (IBD/EURD).

Agomelatine is approved in more than 80 countries.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

During the assessment of PSUR 5 (period 20.02.2011-19.02.2012) 6 cases of hepatic failure were discovered (updated to 8 cases in the variation procedure that followed). For some of these, non-compliance with recommendations in the SmPC was noticed, and some seemed to occur in connection with dose increase (from 25 to 50 mg). This led to updates to the SmPC recommending that monitoring of liver enzymes should be performed when the dosage is increased and with the same intervals as recommended when treatment is started (i.e. after 3, 6, 12 and 24 weeks). Additionally, an increase in the incidence of transaminase elevations > 3 ULN was noted (from 1,2% and 1,7% to 1,4% and 2,5% on 25 and 50 mg, respectively). A DHPC was submitted in October 2012 with information that severe hepatotoxic reactions, including hepatic failure, had been reported. Prescribers were informed about the updates to the SmPC and reminded to strictly adhere to the treatment recommendations for monitoring of the liver function. In December 2012 updated educational material was submitted, including a monitoring scheme to be used as a tool for the physician to document that the recommended liver monitoring has been performed in each individual patient.

To document the effectiveness of the DHPC and educational material, the MAH is currently performing a prescription survey in France, Germany, Greece and Spain (results to be submitted to EMA in December 2013).

In October 2012, angioedema was detected as a signal in the Eudravigilance database. CHMP adopted the PRAC recommendation to include urticaria, face oedema and angioedema as ADRs in section 4.8 of the SPC.

In February 2013, a signal of QT-prolongation was generated in the Eudravigilance database. QT-prolongation has also been generated as a signal in the WHO-database (SIGNAL May 2013, Analyses of Reports in the global ICSR Database-Vigibase).

1.3.2. Changes to reference safety information

The RSI in effect at the end of the reporting period, corresponds to section 4.3 to 4.9 of the SmPC proposed in the context of finalization of the variation related to elderly patients. It is dated 15.02.2013.

Updates to the RSI in the current PSUR period:

Section 4.4.

- information that cases of severe hepatic ADRs, including hepatic failure and elevations of liver transaminases > 10 ULN, have been reported.
- Recommendations that monitoring of liver enzymes should be performed when the dose is increased (from 25 to 50 mg) and with the same intervals as recommended when treatment is initiated (i.e. after 3, 6, 12 and 24 weeks).
- Statement to stop treatment immediately if signs or symptoms of potential liver injury occur. Signs and symptoms were described.
- information that no effect is documented in patients ≥ 75 years and that agomelatine is not recommended in this age group

Section 4.5

Information that the following agents can interact with agomelatine:

- ofloxacin (inhibitor of CYP1A2)
- rifampicin (inducer of CYP1A2, CYP2C9, CYP2C19)
- smoking (inducer of CYP1A2)

Section 4.8:

The following ADRs were added:

- hepatic failure, jaundice, vomiting, weight increased, weight decreased, urticaria, angioedema and face oedema

The frequency of elevated liver transaminases was updated

Based on information in the current PSUR (6), the MAH proposes to include "restless leg syndrome" as an ADR in section 4.8. (See below discussions and Annex 1)

No further risk minimisation measures are proposed.

1.3.3. Estimated exposure and use patterns

Cumulative subject exposure in clinical trials

A total of 14 156 patients were involved in the 47 completed phase II or III clinical trials conducted during the agomelatine development plan and 3701 patients were involved in phase IV studies. In addition, at the data-lock point of the report, 659 additional patients were involved in the ongoing studies.

The following table displays the number of patients and exposure based on follow-up duration, expressed in patient-months, in phase II, III and IV studies:

Table (5.1) 1 - Number of patients and exposure by treatment groups and according to the clinical trial status

		All agomelatine	Agomelatine 25 or 50 mg	Placebo	All active comparators
Phase II/III					
Completed (but CL3.073)	N	9 364	8 410	1 851	2 604
	(PM)	44 610.7	42 252.7	5 757.1	9 816.9
CL3.073[(1)]	N	337	337	-	-
	(PM)	1 185.5	1 185.5	-	-
All completed CT*	**N**	**9701**	**8747**	**1851**	**2604**
	(PM)	**45 796.2**	**43 438.2**	**5 757.1**	**9 816.9**
Ongoing**	N	340	340	38	281
	(PM)	856.5	856.5	137.2	520.8
Phase IV***					
Completed	N	3 701	3 701	-	-
	(PM)	13 180.4	13 180.4	-	-

PM: Patients-months.
CT: Clinical trials
[(1)]CL3.073: due to its atypical design (initiation of agomelatine as a relay treatment after SSRI/SNRI immediate or progressive withdrawal), this study was not included in the IAS and presented separately.
* *agomelatine exposition was maximized as only agomelatine exposition period is considered for patients who were treated by both placebo and agomelatine.*
** *CL3.060, CL3.072, CL3.074, CL3.078, CL3.080, CL3.083.*
*** *interventional phase IV studies*

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

		OSS N= 9364 (44610.7 PM)		MDD N= 7967 (39489.2 PM)	
		n	**PM**	**n**	**PM**
Duration					
Cumulative up to 1 month		8268	18.53	7110	18.00
Cumulative up to 3 months		5251	11.77	4592	11.63
Cumulative up to 6 months*		2356	5.28	2152	5.45
Cumulative up to 12 months**		1094	2.45	1094	2.77
Dose of exposure					
1-5 mg		547	858.1	302	488
10 mg		338	1433.6	132	518.9
25 mg		5690	26376.6	5237	24432.2
50 mg		2720	15876.1	2283	14036.4
100 mg		69	66.2	14	13.7
Age group (years)					
[18-65 [		8325	40391.2	7456	37145.0
[65-75 [		646	2724.7	407	1947.0
[75-85 [		294	1037.8	100	384.5
≥ 85		99	457.0	4	12.7
Gender					
Male		2917	13744.9	2397	11958.3
Female		6447	30865.8	5570	27530.9
Special populations					
Renal impairment					
	<50 mL/min	270	1074.7	56	225.7
	[50-80] mL/min	2476	10779.6	1915	8732.1
	> 80 mL/min	4624	20342.8	4028	18174.8
	missing	1994	12413.5	1968	12356.6
Hepatic impairment		Not included in clinical studies			
Pregnant women#					
Lactating women		Not included in clinical studies			
Relevant comorbidities					
Obesity (BMI ≥ 30 kg/m²)		1999	10900.9	1809	10169.2
Alcohol consumers		2847	13341.0	2282	11170.9
Smokers		1944	8705.2	1724	7901.8

* *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 (PT)
*PM: Incidence expressed per 100 Patients-Months : (n/PT)*100*

1.3.4. Data in summary tabulations

The following tabulations are appended to this AR:

- Cumulative summary tabulation of serious adverse events in clinical studies
- Numbers of adverse drug reactions by preferred term from post-marketing sources

1.3.5. Summaries of significant findings from clinical trials in the reporting interval

Completed clinical trials

During the period covered by this report, five new clinical studies were analyzed: CL2.067, CL3.069, CL3.070 and CL3.071 and CL3.073.

Efficacy findings

Since MA the MAH has performed six short term studies with different active comparators. These are summarised in the section 4. Benefit evaluation. A renewal of the MA for Valdoxan is currently ongoing. In this connection the CHMP-Rapporteur has summarized results from 13 studies performed after grant of marketing authorisation (including the six studies already mentioned). CHMP opinion/RSI of this renewal is foreseen in July 2013.

Two post commitment studies investigating Agomelatine in the treatment **of Major Depressive Episodes** either in adult (CL3.069) or in elderly (CL3.070) populations, have been performed in the actual PSUR interval.

CL3.069 study (REC 3) aimed at demonstrating the clinical efficacy and safety of at least one of the three dose regimens of agomelatine (10, 25, 25-50 mg/day) versus placebo given once a day for six weeks in out-patients suffering from moderate to severe MDD. A total of 549 patients were enrolled. A total of 505 (92%) patients completed the mandatory W0-W6 period, and 411 (75%) entered the double-blind, optional extension period of 18 weeks.

According to the current SmPC, the dose may be increased to 50 mg/day if no improvement is seen after two weeks on 25 mg/day. One of the main objectives of this study was therefore to demonstrate that the 50 mg dose was more efficacious compared to the 25 mg/dose, as this has previously not been shown.

CHMP concluded that the study does not have a design to allow for a conclusion regarding the efficacy of increasing the dose to 50 mg in patients not responding to 25 mg. For the 2 groups (25 mg fixed and 25-50 mg) the results are considered clinically relevant compared to placebo, however, the difference between the two groups is marginal. It was concluded that the data indicated that some patients may still benefit from an increased dose compared to those continuing on the 25 mg dose. However, the risk of liver related ADRs is increased on the higher dose. The MAH has therefore proposed the following for inclusion in section 4.2 of the SmPC:" 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." to reflect the increased risk with the higher dose. This amendment was endorsed by CHMP. Accordingly, the MAH has been requested to apply for a type II variation to include this information in the SPC.

Study CL3.070 (FUM 002), assessed by the CHMP, aimed at studying the efficacy and safety of agomelatine (25-50 mg/day) for 8 weeks in elderly patients suffering from MDD. A total of 218 patients were randomized to either agomelatine 25-50 mg/day or placebo. An optional double-blind extension period up to 16 weeks was scheduled for this study. Out of the 222 randomized patients,

175 (79 %) completed the mandatory W0-W8 period and 146 (66 %) entered the double-blind extension period. The clinical study in patients 65 years and older, revealed a statistically significant difference on the primary endpoint, HAM-D 17, between the agomelatine group and the placebo group in the full analysis set. The clinical relevance seemed modest; however, it was in line with the effect observed for agomelatine in other clinical studies in younger adults. On the contrary, no effect was documented for the sub-group of patients ≥75 years. In addition, the exposure of agomelatine was shown to increase several fold in this age group compared to patients <75 years. The MAH was requested to submit a Type II variation, and the SmPC was amended in order to reflect the results achieved in elderly patients.

Study CL3-20098-073:
This study aimed at comparing 3 different ways to initiate agomelatine after antidepressant treatment by SSRI or SNRI, using the Discontinuation-Emergent Signs and Symptoms check-list: either by immediate substitution or by initiation of agomelatine with 2 different taperings of the previous drug, in depressed out-patients requiring a change in their antidepressant treatment due to an insufficient treatment efficacy (associated or not with poor acceptability).

Group 1: agomelatine 25 mg o.d. and previous antidepressant at therapeutic dose o.d (20 mg for paroxetine, 75 mg for venlafaxine) on the 1st week then at half therapeutic dose on the 2nd week, then placebo on the 3rd week (Long tapering).

Group ½: agomelatine 25 mg o.d. and previous antidepressant at half therapeutic dose o.d. (10 mg for paroxetine, 35.5mg for venlafaxine) on the 1st week, then placebo on the 2nd and 3rd week (Short tapering)

Group 0: agomelatine 25 mg o.d. on the 3 first weeks (Immediate substitution).

MAH's evaluation of the results:
This international, controlled, phase III study conducted in outpatients suffering from major depressive disorder and with insufficient antidepressant treatment efficacy showed that whatever the switch strategy (long tapering, short tapering or immediate substitution), discontinuation symptoms occurred after the previous antidepressant treatment stop: however, discontinuation symptoms were less frequent with long tapering than with short tapering and immediate substitution. This was mainly due to the lower number of patients affected (complementary analysis). Psychic symptoms were the most frequently reported (nervousness/anxiety, agitation, increased dreaming/nightmares, bouts of crying, sudden worsening of mood, trouble sleeping/insomnia). Whatever the switch strategy, patients were markedly improved over time after intake of agomelatine 25 mg, with a high rate of responders despite failure of the previous antidepressant treatment by SSRI or SNRI. Efficacy was similar in all groups after 8 weeks of treatment even if for few criteria (feeling good and some emotions) improvement was found slightly better in patients with immediate substitution than in patients with tapering of the previous AD. For most of efficacy criteria, improvement was clearly less marked when discontinuations symptoms were more frequent. This study thus suggested a direct impact of discontinuations symptoms on efficacy as judged by the physician (CGI), sleep, daytime sleepiness and in a less extent on emotions.

Emergent adverse events were less frequent in patients with long tapering than in patients with short tapering and immediate substitution. This likely reflected the differences in withdrawal symptoms evidenced with the DESS. Globally, the greater the length of time of the tapering, the lower the number of emergent adverse events there was. Regarding biology and other safety criteria, no relevant difference was observed according to the switch strategy.

PRAC position:

The MAH was advised to consider whether treatment recommendations when therapy is switched from another antidepressant therapy (SSRI or SNRI), can be derived from this study. If so, treatment recommendations should be included in the SmPC as this is clinical important information for the prescriber.

Study CL2-20098-067:

This phase II exploratory, multicentre, randomised study conducted in moderate to severe MDD patients and healthy volunteers, investigated the effects of treatment (agomelatine or placebo) on cerebral activation during an emotional stimulus processing paradigm. This was a randomised, double-blind, placebo-controlled study with an open extension period of 6 months with agomelatine (25 mg).Functional MRI Profiles were compared with MRI profiles of healthy volunteers.

MAH's evaluation of the results:

The MAH concludes that agomelatine has an early effect (after 1 week of treatment) on the automatic control of self-referential and emotional processes (translated by decreased activations of ventrolateral prefrontal cortex and the amygdala). This early effect was observed before clinical improvement of symptoms as there was no relevant difference between agomelatine and placebo groups in terms of symptomatic disease. Agomelatine has a later effect (after 7 weeks of treatment) leading to a more balanced allocation between cognitive control and automatic processes of self-referential relevance (translated by decreased activation of dorsolateral prefrontal cortex and an increased activation of ventral anterior cingulate).

Overall the fMRI results suggest that brain changes induced by agomelatine target specific regions involved in self-processing and cognitive regulation of emotion. Agomelatine showed different brain effects at W1 and at W7, suggesting a specific time course of brain changes in order to correct depressive symptoms.

No unexpected adverse events were reported.

Safety findings

An updated Integrated Analysis of Safety (IAS) was performed on a pool of 46 studies coded with MedDRA 15.0 version (cut-off date: 16 November 2012) in order to monitor the risks mentioned in the RMP and to detect potential new signals.

Regarding the known identified hepatic risk monitored in the framework of the RMP and based on the overall agomelatine clinical trial database, a higher incidence (1.75%) of transaminases elevation (> 3ULN) has been observed after administration of agomelatine 25-50 mg (1.34% on agomelatine 25 mg, 2.51% on agomelatine 50 mg) as compared to placebo (0.50%).

PRAC comments:

The updated incidences of elevated liver transaminases > 3 ULN are in accordance with incidences calculated previously from pooled clinical trials (2.5% for the 50 mg dose compared with 1.4% for the 25 mg dose).

This updated IAS confirmed the known safety profile of agomelatine.

No unexpected safety findings were observed in clinical studies completed during the reported period.

Ongoing clinical trials

During the period of this PSUR, 7 clinical efficacy and safety interventional studies with agomelatine were in progress, one in healthy volunteers CL1.081 and six in patients (CL2.072, CL3.060, CL3.074, CL3.078, CL3.080 and CL3.083). Around 300 subjects were exposed to agomelatine during the reported period.

Blind Safety Analysis (BSA) was performed in December 2012, on four pooled ongoing studies (CL2.072, CL3.060, CL3.080 and CL3.083) in order to monitor the risks mentioned in the RMP and to detect potential new signals. The safety analysis performed in blind condition showed no new or unexpected findings.

Regarding the identified risk monitored in the framework of the RMP, three patients experienced a transaminases increase > 3 ULN. Among these 3 cases, 2 patients (from CL3.083 study) had a transaminases increase between 3-5 ULN, and 1 (from CL3.060 study) had transaminase increase > 10 ULN. Two cases were evaluated by the MAH's Liver Safety Committee, as possibly related and one as unlikely related to the treatment.

Five cases of transaminase increase > 3ULN from CL3.069 study have been unblinded during the period of this PSUR (2 cases under agomelatine 50 mg, 2 under 25 mg and 1 case under 10 mg). Those cases are taken into account in the last updated Integrated Analysis of Safety (for cumulative re-estimated incidence of transaminase increase > 3ULN presented in the relevant section below). One case of transaminase increase > 3 ULN from CL3.074 study, unblinded during the reported period, occurred under sertraline treatment.

PRAC comments:

The reports of increased transaminases from these studies are similar to the reports of hepatotoxicity that has been seen previously with agomelatine. Consequently, no new information with regards to hepatotoxicity was identified from these reports.

1.3.6. Findings from non-interventional studies

One prospective observational study (CLE-20098-068) conducted according to the European Risk Management Plan (EuRMP), was ongoing with 6 365 patients included at the data-lock point of the report. The objective is to evaluate the safety of agomelatine in current medical practice in depressed patients, with focus on hepatobiliary disorders, suicidality, skin events, patients with known renal impairment and elderly patients. This study allows an active surveillance of agomelatine on an international scale in usual medical practice.

Transaminases increase:

Twenty seven (27) cases of transaminases increase >3ULN were reported, 4 were considered as serious and related to agomelatine.

Out of the 27 patients, 16 had one value ranging between (3-5 ULN), nine (9) patients had one value ranging (5-10 ULN) and two (2) patients had one value > 10 ULN.

Transaminases increase occurred in 17 female patients and 10 male patients. The median time to detection was 45 days (range 8-168 days). Eight patients already had abnormal transaminases values at baseline. Neither specific signs nor symptoms were reported except for one patient with jaundice related to hepatitis C.

Most of the patients had confounding factors for transaminases increase, mainly overweight/obesity (13 cases), and/or concomitant drugs with known potential hepatotoxicity (14 cases). Six patients had medical history of alcohol abuse or past of alcohol abuse; three other patients had pre-existing liver disease (1 fatty liver, 2 liver steatosis). One other patient with a known alcohol abuse and chronic hepatitis C had a liver fibrosis and a hepatomegaly reported in the medical history. Two patients presented diabetes at baseline.

Agomelatine was withdrawn in 24 patients (23 recovered or recovering), and maintained in 3 cases (all recovered).

PRAC comments:

Overall, the 27 cases of transaminases increased from this non-interventional study seemed to follow the pattern of such reactions that is known to occur with agomelatine. In many of the cases the patients had risk factors for hepatic injury, such as overweight, diabetes and alcohol abuse, which is already included in a warning in section 4.4 of the SmPC. In some of the cases, it was noted that the patients had an increase in transaminases exceeding 3 X upper limit of normal at baseline, thus treatment should not have been initiated had the recommendations in the SmPC been strictly adhered to. Overall, it is considered that no new information has been identified from these reports.

Suicide events:

Thirty three (33) suicide events were reported in 29 patients during the period of the PSUR, whatever the seriousness and relationship. Among these 33 events, there were: 1 completed suicide, 9 suicidal attempts, 5 intentional overdoses, 2 intentional self injuries, 1 suicidal behaviour, and 15 cases of suicidal ideation.

Three (3) suicidal events were considered as serious and related to the treatment: 1 case of suicide attempts with an intentional overdose and 2 cases of suicidal ideation/behaviour.

Skin reaction:

One case of Rash and one case of Cold sweat were assessed as serious and related to agomelatine.

Pregnancy: Three cases of pregnancies were reported (including one pregnancy with spontaneous abortion considered by the physician as serious and related).

Other Serious Adverse Drug Reactions: 22 patients experienced a serious adverse drug reaction (63 events) during the covered period, not including cases of transaminase increase, suicide events or skin reactions. The most frequently reported events were: fatigue and asthenia (6 patients), dizziness and vertigo (6 patients), nausea (5 patients), headache and migraine (5 patients) and depression or depressed mood (4 patients).

The MAH concludes that no new relevant safety information was identified from the ongoing cohort study.

1.3.7. Lack of efficacy in controlled clinical trials

In study **CL3.070** efficacy was proven in patients < 75 years, but not in patients ≥ 75 years (FUM 002). Further information about this study is given in section 2.3.5.

1.3.8. Late-breaking information

No new important information.

1.4. Discussion and conclusions on PSUR data

Agomelatine is approved in more than 80 countries.

During the PSUR-period, a signal of angioedema was generated in the EV database. Following recommendation from PRAC, angioedema, urticaria and face oedema were included as ADRs in section 4.8 of the SmPC.

Further, a signal of QT-prolongation was generated in EV, as well as in the WHO-database.

This signal was under evaluation at the time of this report.

2. Signal and risk evaluation

- **Tabular overview of signals: new, on-going or closed during the reporting interval (20.02.2012-19.02.2013)**

The tabular overview is appended to this PSUR.

2.1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	*Hepatotoxic reactions* *Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)*
Important potential risks	*Skin reactions* *Suicide*
Important missing information	*Paediatric age group (< 18)* *Elderly (> 75 years)* *Pregnancy* *Lactation* *Hepatic impairment* *Severe or moderate renal impairment*

Signal evaluation

A signal detection process is performed at least every 3 months according to internal procedure. All worldwide sources are considered.

Different factors are taken into account in this process such as chronological and semiologicalanalysis of events, association to other listed events, confounding factors, pharmacological, plausibility and disproportionality analysis in the MAH database.

The methods of signal's evaluation include:

- Review of cases and estimated incidence,

- Non clinical and clinical study results,

- Literature searches,

- Epidemiological data and post-authorization studies results,

- Disproportionality analysis in MAH database if relevant,

- Any other information provided in the context of regulatory procedures or ongoing benefit-risk monitoring if applicable,

- Other ICSR with similar events terms

An Integrated Analysis of Safety(IAS) of the clinical data was performed through 2 data sets:

The Overall Safety Set (OSS) includes all completed phase II and phase III S20098 studies in adults. This set includes all Servier studies and, since 2011 clinical studies performed by a Servier licensee whatever patient's treatment duration.

The Overall Double Blind Placebo-Controlled Set (OSS PC DB) includes completed placebo-controlled studies (26 studies), with a focus on the marketed 25-50mg doses. It corresponds to a set of patient with the same treatment duration. It represents a total of 7 096 patients. This analysis was performed to overcome the bias due to the difference of treatment duration in the OSS.

During the period covered by this report, two IAS were specifically reviewed:

- IAS 2011 groups together 44 studies with a total of 13 228 patients,

- IAS 2012 groups together 46 studies with a total of 13 819 patients.

Events under close monitoring

The following events have been under close monitoring in the actual PSUR period:

Confusion, tinnitus, pancreatitis, hyponatraemia/SIADH, convulsion, blood bilirubin increased, muscular events and blood pressure increased, urticaria, alopecia, palpitations, oedema peripheral, panic attacks, muscle spasm and tremor.

Confusion, tinnitus, pancreatitis, hyponatraemia/SIADH, convulsion, blood bilirubin increased, muscular events and blood pressure increased.

Following PSUR 5 the MAH was requested to perform a cumulative review of these cases and assess the causality with agomelatine. If relevant, the MAH should consider the need for implementing risk minimisation measures.

This was addressed in SIAMED PAC No. PSU 011.1.

It was concluded that the information was too scarce to evaluate the causality between the events and agomelatine. Consequently, the MAH was requested to present an updated cumulative overview of these events based on relevant SMQ. In particular, the following information was requested:

a) Cases with positive rechallenge, including narratives

b) Cases with positive dechallenge, including narratives

c) Cases recovering during continuous treatment

d) Cases where symptoms increased in severity when agomelatine treatment was added to other concomitant treatment likely to induce the event

Further on, the MAH was asked to discuss with reference to the SmPC-guidelines, if there is evidence to include any of the events in the SmPC.

Alopecia, palpitations, oedema peripheral, panic attacks, muscle spasm and tremor

Following PSUR 5 the MAH was requested to discuss these events in the next PSUR.

Confusion

CLINICAL RELEVANCE	
Number of cases since MA	44 (41 HCP) (6.6 / 100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 14/44 Within 1 month: 6/44 Within 3 months: 7/44 Unknown: 17/44
Class effect	Unknown
Biological/Pharmacological plausibility	Unknown
Causality assessment Dechallenge/Rechallenge	Doubtful: 44/44 Positive dechallenge: 31/44; No positive rechallenge
Alternative explanation	Relevant medical history: 13/44 • Confusion, Dementia, Psychosis: 7/44 • Memory impairment or Attention disorder: 2/44 • Bipolar disorder: 3/44 • Alcohol abuse: 5/44 Relevant context: 25/44 • Recent change in concomitant treatment, including antidepressant or benzodiazepin withdrawal: 4/44 • Mania/Hypomania/Dysphoria: 4/44 • Infection: 2/44 • Somnolence: 3/44 • Hallucination, Nightmare: 7/44 • Cerebrovascular accident: 1/44 • Hyponatraemia: 1/44 (no SSRI associated) • Alcohol abuse: 2/44 • Recent vaccine administration: 1/44 Concomitant drugs: 26/44
Serious (Fatal) cases	20/44 (0)
Outcome of the event	Recovered: 34/44 Recovering: 2/44 Not recovered: 1/44 Unknown: 6/44 Fatal: 1/44 (1 completed suicide)
Noveltv of the reaction	Yes

Clinical data	No significant between-group difference in IAS 2011: OSS: 0.12% Agomelatine *vs.* 0.12% placebo.
Post authorization studies / Patient's support programs	CLE-20098-068 (3611 patients treated / average treatment duration: 131 days) 1 patient presented emergent Confusional state No safety issue identified
Literature findings	No data found associated to Agomelatine
Discussion	Post-marketing data: - 44 cases (moderate incidence: 6.6/100 000 PY) - No case with imputability assessed as possible or likely. - 68 % of patients had a r elevant context, concomitant treatments or medical history likely to induce confusional state - Favourable evolution in 95% of cases with documented outcome Clinical trial data: - No significant between-group difference in IAS 2011 Other sources: - No relevant reports found in the literature - No safety concern arose from PASS and non-clinical data
Conclusion	False signal

PRAC comments:

When the signal was closed on 19.08.2012, 44 events had been reported to the MAH. Later additional 12 cases have been reported.

Review of the narratives indicates that these cases to a great extent could be possibly attributed to agomelatine. However, we agree that many confounding factors are present.

Data from pooled clinical trials (Integrated analysis of safety) show no significant difference in incidence of confusion between agomelatine and placebo. The cumulative incidence since grant of MA has decreased since the previous PSUR (no 5) period (from 7.8/100 000 PY to 6.6/100 000 PY).

The PRAC endorses the position that confusion should no longer be under close monitoring.

Tinnitus

CLINICAL RELEVANCE	
Number of cases since MA	52 (39 HCP cases) (6.1/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 2 days: 17/52 3 days to 1 week: 9/52 1 week to one month: 7/52 > 1 month: 7/52 Unknown: 12/52
Class effect	Unknown
Biological/Pharmacological plausibility	No safety issue identified No pharmacological plausibility.
Causality assessment Dechallenge/Rechallenge	Doubtful: 50/52 Likely: 2/52 Positive dechallenge: 18/52 Positive rechallenge: 2/52
Alternative explanation	Relevant medical history: 11/52 • Tinnitus: 10/52 • Hypertension: 2/52 Relevant context: 19/52 • Deafness / Hearing impaired: 3/52 • Hypoacusis / Hyperacusis: 2/52 • Dizziness / Vertigo/ Vasospasm: 8/52 • Nausea: 6/52 • Recovery period of seizure: 1/52 • Ear fungal infection and otitis: 1/52 Concomitant drugs: 15/52 • SSRI: 5/52 Withdrawn but still suggestive onset latency: 3/52 • Ciprofloxacine : 2/52 • Venlafaxine : 4/52
Serious (Fatal) cases	11/52 (0)
Outcome of the event	Recovered: 20/52 Recovering: 4/52 Not recovered: 16/52 Unknown: 12/52

AVAILAILITY OF OTHER RELEVANT SOURCES	
Pharmacological / non clinical data	No safety issue identified
Clinical data	No significant between-group difference in IAS 2012: • OSS: 1.57% Agomelatine *vs.* 0.81% placebo *(NS) vs.* 1.15% SSRI • OSS DB PC: 0.30% Agomelatine 25-50 mg *vs.* placebo 0.21% *vs.* 0.57% SSRI *(p= 0.598)*
Disproportionality analysis	Higher with AGOMELATINE in comparison to all other Servier drugs (0.35 vs 0.16%, respectively)
Post authorization studies / Patient's support programs	CLE-20098-068 (4246 patients treated / average treatment duration: 168 days) 5 patients presented emergent Tinnitus. No safety issue identified
Literature findings	Tinnitus is a common symptom that demonstrates a significant comorbidity with depression. Neuroimaging studies confirm the existence of neural circuits that are activated both in depression and tinnitus (alteration of the HPA-axis, hyperactive dorsal cochlear nucleus, impaired hippocampal neurogenesis, BDNF as common susceptibility factor). (Langguth, 2011, Roberts 2011).
Discussion	Post-marketing data: - 52 cases (Low incidence 6.1/100 000 PY) - 54% of patients had relevant context, medical history or concomitant medication that could explain tinnitus. - Two cases with imputability assessed as likely in patients presenting relevant past medical history. - No case with imputability assessed as possible. Clinical trial data: - No significant between-group difference in IAS 2012. Other sources: - Literature showed that tinnitus is a common symptom associated with depression. - No relevant reports found in the literature - No safety concern arose from PASS and non-clinical data - No pharmacological/biological plausibility found
Conclusion	False signal

Some cases indicating a causal relationship with agomelatine.

*S1000*****

This case was received from a Psychiatrist.

The patient was a 65-year-old female with a medical history of Cerebrovascular accident in SEP-2009. She was treated with VALDOXAN 25mg daily for Anxious depression since 2010 (exact start date unknown). On 23-AUG-2010 Valdoxan daily dosage was increased to 50mg.

Concomitant treatments included Calcitriol, Calcium, Levothyroxine, Acetylsalicylic acid (75mg daily since SEP-2009), Atorvastatin, Valproate (750mg daily since JUN-2004), Zolpidem and Cafeine / Dextropropoxyphene / Paracetamol.

Previous antidepressant treatment included Fluoxetine which was progressively withdrawn.

In 2010, in the month after the increase of Valdoxan daily dosage to 50mg, she experienced Ear buzzing and ringing. She also experienced Electric shock and tingling sensation in head.

Valdoxan was decreased to 25 mg daily. Ten days after the dose decrease, she experienced an Anxiodepressive reaction.

Ear buzzing and ringing, Electric shock and tingling sensation in head improved.

Valdoxan was increased again to 50 mg daily. Symptoms reoccurred (Positive rechallenge).

Not recovered at the time of the report

Company's comment: Patient with a medical history of recent cerebrovascular accident. The possibility that tinnitus was a sequelae of this accident was not excluded.

*S1200*****

This case was received from Regulatory Authorities.The patient was a 48-year-old female patient with an unknown medical history.She has been treated with VALDOXAN 25 mg (25 mg daily) since 10-NOV-2011 for depression. Valdoxan was initiated the same day as the patient was hospitalised for an unknown reason.Concomitant medications, if any, were not reported.VALDOXAN daily dosage was increased to 50mg daily at a not specified date.Since 10-NOV-2011, the patient experienced tinnitus.On 01-DEC-2011, she experienced hearing decreased.On 30-JAN-2012, VALDOXAN 50mg daily was stopped.Outcome: Recovering since 30-JAN-2012.Suspected medications (with imputability) according to the Regulatory Authority (doubtful): VALDOXAN 25 mg (C2,S1,I1).

Protocol CLE-20098-068*. [Observational cohort study to evaluate the safety of Agomelatine in standard medical practice in depressed patients. A prospective, observational (non-interventional), international, multicentre cohort study.] Post Authorisation Study.The patient was a 46-year old male with a medical history of borreliosis since 2004 and depression. No alcohol, no tobacco consumption. He had been treated with VALDOXAN (25 mg daily) since 17-DEC-2011 for depression.Previous treatment included Amitriptyline (dose unknown) from 01-JUL-2008 to 17-DEC-2010 for depression.In DEC-2010, shortly after Valdoxan initiation, the patient complained of tinnitus in both ears. A block of atlanto-occipital joints was suspected. Additionally, migraine was suspected.VALDOXAN was stopped on 31-JAN-2011. Treatment with Amitryptilin was re-introduced (dosages, treatment dates not available).Recovered. Investigator's opinion (31-MAR-2011): assessed this case as serious (medically important) and related to Valdoxan due to the time coherence.The questions wether an underlying reason for tinnitus had been found or wether problems with the atlanto-occipital joints could be confirmed, were declared as unsolvable by the investigator.

PRAC comments:

Despite some confounding factors, cases of tinnitus above indicate a possible relationship with agomelatine.

Two additional cases have been reported after the signal was closed, and the total number of cases is now 54.

The incidence of tinnitus has increased since the last PSUR period (from 5.3/100 000 PY to 6.1/100 000) PY.

About half of the events occurred within few days (up to one week) after introducing agomelatine. There are two cases with positive rechallenge, and 18 with positive dechallenge. Four patients had a favourable outcome (recovered or recovering) while agomelatine was maintained at the same dosage.

As stated by the MAH, tinnitus may be associated with depression. Other confounding factors are discussed by the MAH and include tinnitus in the medical history, hypertension, concomitant drugs and recent withdrawal of other antidepressant therapy

Clinical trial data based on IAS 2012, show no significant difference in the incidence of tinnitus between agomelatine and placebo. However, data indicates a trend that the incidence is higher in the agomelatine-group vs placebo group (1,57% vs. 0.81% in the OSS and 0,30% vs. 0,21% in the OSS DB PC-set, respectively).

Analysis of the MAH's database shows disproportionality concerning reports of tinnitus between agomelatine and all the other Servier's drugs (0,35% and 0,16%, respectively).

Tinnitus is labeled for SSRIs and TCAs.

Considering the totality of the available data the PRAC considers that there is sufficient information to conclude that a causal relationship between agomelatin and tinnitus is at least a reasonable possibility. It is suggested that tinnitus should be included in SPC 4.8 as a common adverse reaction.

Pancreatitis

CLINICAL RELEVANCE	
Number of cases since MA	16 (all HCP cases) (2.1/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 2/16 Within 1 month: 4/16 > 1 month: 8/16 Unknown: 2/16
Class effect	Unknown
Biological/Pharmacological plausibility	Unknown
Causality assessment Dechallenge/Rechallenge	Doubtful: 16/16 Positive dechallenge: 9/16 No positive rechallenge
Alternative explanation	Relevant medical history: 3/16 • Alcoholic pancreatitis: 1/16 • Alcohol abuse/Alcohol use: 2/16 Relevant context: 4/16 • Alcoholism: 3/16 • Sphincter of Oddi dysfunction: 1/16 Concomitant drugs: 2/16 • Venlafaxine: 2/16 • Fenofibrate: 1/16
Serious (Fatal) cases	12/16 (0)
Outcome of the event	Recovered: 5/16 Recovered with sequelae: 1/16 Recovering: 3/16 Not recovered: 3/16 Unknown: 4/16

AVAILAILITY OF OTHER RELEVANT SOURCES	
Pharmacological / non clinical data	No safety issue identified
Clinical data	No significant between-group difference in IAS 2012: OSS: 0.02 % Agomelatine 25-50mg *vs.* 0% Placebo
Disproportionality analysis	Similar with Agomelatine in comparison to all other Servier drugs (0.12 vs 0.15% respectively)
Post authorization studies / Patient's support programs	CLE-20098-068 (4246 patients treated / average treatment duration: 168 days) 1 patient presented emergent pancreatitis. No safety issue identified
Literature findings	No relevant reports found
Discussion	Post-marketing data: - 16 cases (low incidence 2.1/100 000 PY) - 60 % of cases were poorly documented (5 cases did not provide any lab data and in 5 other cases no investigation were performed) - No case with imputability assessed as possible or likely. Clinical trial data: - No significant between-group difference in IAS 2012 Other sources: - No relevant reports found in the literature - No safety concern arose from PASS and non-clinical data - No data found from epidemiological data - No pharmacological/biological plausibility found.
Conclusion	False signal

PRAC comments:

The cumulative incidence of pancreatitis is 2.1 /100 000 PY compared with 2.3 /100 000 PY after the previous PSUR (5) period.

The PRAC agrees with the MAH that in some cases, the diagnosis of pancreatitis cannot be confirmed, as sufficient investigations are lacking. In at least two cases, the diagnosis of pancreatitis can be excluded.

One patient was diagnosed with exudative pancreatitis (several drugs could be suspected). Agomelatine was reintroduced, and the patient was discharged after two weeks in hospital (negative rechallenge).

In one case the patient had previously experienced alcoholic pancreatitis, as well as toxic pancreatitis related to olanzapine.

In another case exudative pancreatitis was diagnosed after the first intake of agomelatine.

The PRAC accepts the MAH's conclusion that so far there is little evidence to support an association between agomelatine and pancreatitis. However, due to the severity of this condition, the PRAC considers that pancreatitis should remain under close monitoring.

Hyponatraemia (including SIADH)

CLINICAL RELEVANCE	
Number of cases since MA	24 (all HCP cases) (3.1/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 2/24 Within 1 month: 9/24 > 1 month: 10/24 Unknown: 3/24
Class effect	Unknown
Biological/Pharmacological plausibility	Unknown
Causality assessment Dechallenge/Rechallenge	Doubtful: 21/24 Likely: 3/24 Positive dechallenge: 9/24 Positive rechallenge: 3/24
Alternative explanation	Relevant medical history: 12/24 • Renal failure: 1/24 • Hyponatremia: 6/24 • Inappropriate antidiuretic hormone secretion: 1/24 • Prostatic adenoma: 2/24 • Renal tumour excision: 1/24 • Cardiac failure: 3/24 • Hypothyroidism: 1/24 Relevant context: 2/24 • Dehydration: 2/24 Concomitant drugs: 17/24 • Diuretics: 11/24 • SSRI, Mirtazapine, Morphine: 6/24 • PPIs: 4/24 • ACE: 4/24
Serious (Fatal) cases	13/24 (1)
Outcome of the event	Recovered: 15/24 Recovering: 1/24 Fatal: 1/24 Unknown: 7/24
Novelty of the reaction	Yes

AVAILAILITY OF OTHER RELEVANT SOURCES	
Pharmacological / non clinical data	No safety issue identified
Clinical data	No significant between-group difference in IAS 2012: OSS: Agomelatine 25-50mg : 0.06 % vs Placebo: 0%
Disproportionality analysis	Lower with Agomelatine in comparison to all other Servier drugs (0.15 vs 0.7%, respectively)
Post authorization studies / Patient's support programs	No safety issue identified
Literature findings	No relevant reports found
Discussion	Post-marketing data: - 24 cases (low incidence 3.1/100 000 PY) - 92% of patients had a relevant context, medical history or concomitant medication that could explain hyponatremia. - Three cases with imputability assessed as likely which were inadequately documented. - No case with imputability assessed as possible. - Favourable evolution in 94% of cases with documented outcome. Clinical trial data: - No significant between-group difference in IAS 2012 Other sources: - No relevant reports found in the literature - No safety concern arose from PASS and non-clinical data - No data found from epidemiological data - No pharmacological/biological plausibility found.
Conclusion	False signal

S1100**** – positive rechallenge

This case was received from the Regulatory Authorities and then from a Psychiatrist.

The patient was a 78-year-old female with a medical history of microvascular ischaemia, depression and hyponatraemia with previous antidepressant (Mirtazapine). She had been treated with VALDOXAN (25 mg daily) for depression since the beginning of 2011. Concomitant treatments included Acetylsalicylic acid, Ramipril, Alendronate, Latanoprost / Timolol, Calcium and Ciprofloxacin (1000mg daily).

On 03-JUN-2011, she experienced hyponatraemia (no biological value reported). The patient was admitted to hospital and VALDOXAN was stopped. No treatment was prescribed. Recovered on 12-JUN-2011 (positive dechallenge). VALDOXAN (50 mg daily) was reintroduced on 13-JUN-2011 and blood sodium decreased again (positive rechallenge).

VALDOXAN was stopped and the patient was discharged without any antidepressant. Recovered. According to the physician, the patient was vulnerable to low sodium levels. Company's comment: Patient with a medical history of hyponatraemia and concomitantly treated with Alendronate, which is known to induce hyponatraemia.

S1200****-positive rechallenge

This case was received from the Regulatory Authorities.The patient was a 67-year-old female with a medical history of arterial hypertension. She has been treated since 11-APR-2012 with VALDOXAN (25 mg daily), associated with OLMESARTAN / HYDROCHLOROTHIAZIDE (40 mg / 12.5 mg daily), FUROSEMIDE, Potassium, Nebivolol, Risedronic acid and Tramadol / Paracetamol since 2005. No information on previous medication, if any.

In APR-2010, blood sodium was normal.

On 27-APR-2012, lab tests showed blood sodium 119 mmol/L.

On 28-APR-2012, lab tests showed blood sodium 109 mmol/L. The patient was hospitalized for hyponatraemia. OLMESARTAN / HYDROCHLOROTHIAZIDE was stopped.

Blood sodium then increased to 128mmol/L on 08-MAY-2012.

VALDOXAN was stopped on 09-MAY-2012. FUROSEMIDE was maintained. Blood sodium then increased to 139mmol/L on 17-MAY-2012 (136 mmol/L on 24-MAY-2012).

The patient was discharged on 01-JUN-2012 and VALDOXAN was reintroduced.

On 11-JUN-2012, the patient was hospitalized for disturbance of consciousness (Glasgow 12) and general physical health deterioration. Blood sodium was 103 mmol/L. Natriuresis 69 mmol/L. Consciousness state then worsened with onset of coma (Glasgow 8). Sodium (IV) was prescribed.

On 13-JUN-2012, blood sodium was 136 mmol/L. The patient presented with left basal pneumopathy.

On 16-JUN-2012, the situation worsened and the patient died on 17-JUN-2012. Fatal outcome.

Suspected medications (with imputability) according to the Regulatory Authority for the event "Hyponatremia": VALDOXAN (C3, S1, I3)/Likely, OLMESARTAN / HYDROCHLOROTHIAZIDE (C1, S2, I1)/doubtful and FUROSEMIDE (C1, S2, I1)/doubtful.

S1200**** – positive dechallenge

This case was received from a Psychiatrist. The patient was a 60-year-old female patient with a medical history of alcoholism and depression. She has been treated with VALDOXAN 25 mg (25 mg daily) for depression since JAN-2012. Concomitant medications included: Hydroxyzine and Zolpidem, indication, daily dose and start date were not reported. At initiation of treatment with VALDOXAN 25 mg, laboratory values were normal, including blood sodium (actual values were not provided). On an unspecified date at the end of FEB-2012, the patient experienced hyponatremia (120 mmol/L). In FEB-2012, VALDOXAN 25 mg was stopped. Two weeks after VALDOXAN 25 mg withdrawal, blood sodium was within the normal range (values were not provided). Outcome: Recovered.

PRAC comments:

In most of the cases agomelatine can possibly be related to hyponatraemia. However, it is recognized that most cases have confounding factors, like use of other substances being associated with hyponatraemia (for instance diuretics and antidepressants). This also applies to the three cases with positive rechallenge, although agomelatine remains the main suspected agent. Some of the patients had a medical history making them vulnerable to hyponatraemia. In four cases outcome was favourable although agomelatine was maintained at the same dose.

The MAH informed that six additional reports have been received after the above analysis, but considered that they did not raise any new safety concern. Accordingly, the total number of

hyponatraemia cases reported to the MAH was thirty (30).

The cumulative incidence since MA is 3.1/100 000 PY (2.9/100 000 PY in the previous PSUR (5) period.

Hyponatraemia is a potential serious condition. Clinical trial data based on IAS 2012, show no significant difference in the incidence of hyponatraemia between agomelatine (0.06%) and placebo group (0%).

Considering the totality of the available data, the PRAC considered that there was some evidence indicating a causal relationship between agomelatine and hyponatraemia. To further elucidate this issue, the MAH was asked to submit all narratives that had previously not been submitted, including narratives for the six new cases of hyponatraemia.

Hyponatraemia is labeled for SSRIs and SNRIs.

Convulsions

Results

CLINICAL RELEVANCE	
Number of cases since MA	33 (29 HCP cases) (4.3/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 15/33 Within 1 month: 7/33 > 1 month: 7/33 Unknown: 4/33
Class effect	Unknown
Biological/Pharmacological plausibility	Unknown
Causality assessment Dechallenge/Rechallenge	Doubtful: 32/33 Likely: 1/33 Positive dechallenge: 19/33 Positive rechallenge: 1/33
Alternative explanation	Relevant medical history: 15/33 • Epilepsy / Convulsion: 12/33 • Cerebrovascular accident: 3/33 • Alcoholism: 2/33 Relevant context: 6/33 • Benzodiazepine abrupt discontinuation or tapering: 2/33 • Discontinuation of antiepileptic treatment: 2/33 • Worsening of epilepsy: 1/33 • Diabetic hyperosmolar coma: 1/33 Concomitant drugs: 16/33
Serious (Fatal) cases	30/33 (1, fatal outcome due to diabetic hyperosmolar coma).
Outcome of the event	Recovered: 25/33 Not recovered: 1/33 (patient died later from diabetic hyperosmolar coma) Unknown: 7/33
Novelty of the reaction	Yes

AVAILAILITY OF OTHER RELEVANT SOURCES	
Pharmacological / non clinical data	No pharmacological plausibility. At 128mg/kg, Agomelatine exhibited a moderate anticonvulsant activity in mice. In the rat, Agomelatine dose-dependently increased the ECS threshold. The effects were statistically significant and marked at > 64mg/kg.
Clinical data	No significant between-group difference in IAS 2012: OSS: 0.06 % Agomelatine 25-50 mg *vs* 0.0 % Placebo
Disproportionality analysis	Similar with AGOMELATINE in comparison to all other Servier drugs (0.3 vs 0.18%, respectively)
Post authorization studies / Patient's support programs	CLE-20098-068 (4246 patients treated / average treatment duration: 168 days) 3 patients presented emergent convulsions. No safety issue identified
Literature findings	No relevant reports found
Discussion	Post-marketing data: - 33 cases (low incidence 4.3/100 000 PY) - 64% of patients had a relevant context, medical history or concomitant medication that could explain convulsions. - One case with imputability assessed as likely in a patient with a medical history of epilepsy, this case was poorly documented. - No case with imputability assessed as possible. - Favourable evolution in 96% of the cases with documented outcome. Clinical trial data: - No significant between-group difference in IAS 2012 Other sources: - No safety concern arose from PASS - No relevant reports found in literature - Preclinical data showed rather an anticonvulsant effect of Agomelatine. - No data found from epidemiological data - No pharmacological/biological plausibility found.
Conclusion	False signal

Presentation of some cases:

*S1100**** – positive rechallenge*

This case was received from a Psychiatrist.

The patient was a 44-year-old female, with a medical history of insufficiently controlled hypotension, hyperthyroidism, anaemia with severe fatigue, depressive episode and epilepsy (treated by antiepileptics in the past). She was treated with VALDOXAN 25mg daily for depression since 05-MAY-2011.

In 2003, neurological examination was performed and the diagnosis of epilepsy was not confirmed. As a consequence, antiepileptics were stopped. But the patient still experienced epilepsy crisis from time to time (the last one in MAR-2011).

After Valdoxan introduction, on 17-MAY-2011 the patient had an episode of epilepsy, or a cardiac syncope (according to the physician from the emergency department). Neurological and cardiologic investigations were performed. The diagnosis of epilepsy was not confirmed, but could not be excluded. VALDOXAN was stopped and no new epileptic episode occurred.

After re-introduction of Valdoxan by the patient's initiative, a new epileptic episode occurred. (Positive rechallenge). The reporter wondered if Valdoxan could have lowered the convulsive threshold in this patient (suspected mechanism).

VALDOXAN was maintained.

Recovered.

Company's comment: Patient with a medical history of convulsions. Investigations performed were not conclusive. Epilepsy (occurring before Valdoxan initiation) was not excluded.

PRAC comments:

A positive rechallenge was seen. However, agomelatine was maintained, and no information about the outcome is available

S1101**** – positive dechallenge:

This case was received from a Physician. The patient was a 50-year-old female, with a medical history of depression and epilepsy for years (date of onset unspecified). She had been treated with VALDOXAN (25 mg daily), for depression, since OCT-2011 (exact date unknown). No previous antidepressant medication. Concomitant medications included Levetiracetam (2000 mg daily) and Carbamazepine (600 mg daily), as long-term treatment of epilepsy. Under these treatments, the patient was free of attacks for a long time.In OCT-2011, one week after Valdoxan initiation, the patient experienced generalized seizure attacks with unconsciousness, urine loss and mucosal bites up to three times a week. VALDOXAN was stopped in NOV-2011, after two weeks of treatment. No seizure occurred since then (recovered). The reporter assessed the event as life-threatening.

S1200****- positive dechallenge:

This case was received from a Physician. The patient was a 47-year-old female with no relevant medical history. She has been treated since 03-APR-2012 with VALDOXAN (25 mg daily) for depression. No concomitant medication was reported. On 29-APR-2012, the patient was hospitalised for epilepsy. Neurological exam and ECG were normal. VALDOXAN was stopped. Outcome: Recovered.

PRAC comments:

Additional three cases were been reported after the MAH's analysis. Accordingly, a total of 36 cases of convulsions have been reported since MA. The cumulative incidence since grant of MA is 4.3/ 100 000 PY (4.7/100 000 PY following the previous PSUR (5) period).

The conclusion whether agomelatine can induce convulsions is a difficult one to make.

Nearly half of the cases occurred within the first week of therapy which can support an association. Twelve (12) patients had epilepsy/convulsions in their medical history. However, information is often insufficient to evaluate whether the condition was under control before agomelatine was introduced. At least one patient(S1101**** – described above) had been stabile on anticonvulsant therapy for a long time, but experienced several generalized seizure attacks with unconsciousness after starting with agomelatine. The reporter assessed the reactions as life-threatening. The patient recovered upon agomelatine withdrawal.

In some cases the patient had recently stopped taking SSRI before agomelatine was introduced with possible impact on their threshold for convulsions.

Out of the 38 cases of Convulsion received since Market Authorisation, 4 patients had a favourable outcome (recovered or recovering) while Agomelatine was maintained at the same dosage (narratives not provided).

Clinical trial data based on IAS 2012, show no significant difference in the incidence of convulsions between agomelatine and placebo. However, data indicates a trend that the incidence is higher in the agomelatine-group (0.06%) vs placebo group (0%).

Convulsions is labeled for SSRIs and SNRIs.

Considering the totality of the available data the PRAC considered that there was sufficient

information to conclude that a causal relationship between agomelatine and convulsions is at least a reasonable possibility. It was suggested that convulsions should be included in SPC 4.8 as a rare adverse reaction.

Myalgia

CLINICAL RELEVANCE	
Number of cases since MA	55 (41 HCP cases) (8.1/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 17/55 Within 1 month: 24/55 > 1 month: 8/55 Unknown: 6/55
Class effect	Unknown
Biological/Pharmacological plausibility	Unknown
Causality assessment:	Doubtful: 52/55 Likely: 3/55 Positive dechallenge: 29/55 Positive rechallenge: 3/55
Alternative explanation	Relevant medical history: 10/55 • Hypothyroidism, goitre, thyroid neoplasm: 4/55 • Sciatica: 1/55 • Muscle spasms, muscle tightness, tendonitis, back pain: 5/55 Relevant context: 16/55 • Back pain (listed event): 5/55 • Intervertebral disc protrusion: 1/55 • Muscle spasms, muscle tightness, muscle injury, musculoskeletal stiffness: 4/55 • Fibromyalgia: 1/55 • Bladder cancer and prostate cancer: 1/55 • Restless leg syndrome: 1/55 • Thyroiditis subacute: 1/55 • Pyrexia or influenza: 2/55 • Intensive sport activity: 1/55 Concomitant drugs: 10/55 • Statins: 2/55
Serious (Fatal) cases	11/55 (0)
Outcome of the events	Recovered: 33/55 Recovering: 5/55
AVAILAILITY OF OTHER RELEVANT SOURCES	
Pharmacological / non clinical data	No safety issue identified
Clinical data	No significant between-group difference in IAS 2012: OSS: 0.77% Agomelatine *vs.* 0.43% placebo (*p=0.127*) OSS DB PC: 0.40% Agomelatine *vs.* 0.64% placebo (*p=0.249*)
Post authorization studies / Patient's support programs	CLE-20098-068 (3611 patients treated / average treatment duration: 131 days) 5 patients presented emergent Myalgia No safety issue identified
Literature findings	No relevant reports found
Epidemiologica data	Within 3 and 6 months following a diagnosis of MDD, the incident rates of myalgia (including fibromyalgia) were 16.9 and 15.2 per 1000 patients-years respectively *(in-house study using GPRD analyzis between 2000 and 2008,).*

Discussion	Post-marketing data: - 55 cases (moderate incidence 8.1/100 000 PY) - Three cases with imputability assessed as likely: in one case, reappearance of muscle pain while being out of treatment, in another, the patient had medical history of fibromyalgia. - No case with imputability assessed as possible. - Alternative causes found in 57 % of the cases - Favourable evolution in 77% of the cases with documented outcome. Clinical trial data: - No significant between-group difference in IAS 2011. Epidemiological data: - Important incidence of myalgia in depressed patients Other sources: - No relevant reports in the scientific and medical literature - No safety concern arose from PASS and non-clinical data
Conclusion	False signal

PRAC comments:

Seven cases were reported after the MAH's analysis was performed. The cumulative incidence since MA was 8.1/100 000 PY (no data available from the last PSUR (5) period).

Myalgia may be associated with depression and is otherwise prevalent in the population. Accordingly, it was difficult to evaluate whether agomelatine can provoke myalgia in depressed patients.

Based on pooled clinical data (IAS 2012), no significant difference between agomelatine and placebo was seen regarding incidence of myalgia.

The PRAC considered that myalgia should no longer be under close monitoring.

Increased blood pressure

CLINICAL RELEVANCE	
Number of cases since MA	81 (63 HCP cases) (10.6/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	After the first intake: 14/81 2 days to 1 week: 22/81 1 week to 1 month: 23/81 > 1 month: 10/81 Unknown: 11/81 After drug withdrawal : 1/81
Class effect	Unknown
Biological/Pharmacological plausibility	Unknown
Causality assessment Dechallenge/Rechallenge	Doubtful: 77/81 Likely: 4/81 Positive dechallenge: 46/81 Positive rechallenge: 4/81

Alternative explanation	Relevant medical history: 46/81 • Hypertension: 31/81 • Anxiety / Panic attack: 10/81 • Others: Aggression / Agitation / Restlessness / Impulsive behavior / obesity / overweight: 20/81 Relevant context: 37/81 • Agitation: 4/81 • Anxiety / Panic attack: 16/81 • Others : Migraine / Restlessness / Palpitations / Fear / Pregnancy: 20/81 Concomitant drugs: 28/81
Serious (Fatal) cases	37/81 (0)
Outcome of the event	Recovered: 54/81 Recovering: 8/81 Not Recovered: 7/81 Unknown: 12/81
Novelty of the reaction	Yes

AVAILAILITY OF OTHER RELEVANT SOURCES	
Pharmacological / non clinical data	No safety issue identified
Clinical data	No significant between-group difference in IAS 2012: • OSS: 1.57% agomelatine *vs* 0.81% placebo *vs* 1.15% SSRI *vs* 1.92 SNRI • OSS DB PC: 1.11% Agomelatine 25-50mg *vs* 0.89% Placebo *vs* 1.14 % SSRI (*p = 0.492)*
Disproportionality analysis	Similar with AGOMELATINE in comparison to all other Servier drugs (0.6 vs 0.9%, respectively)
Post authorization studies / Patient's support programs	CLE-20098-068 (4246 patients treated / average treatment duration: 168 days) 0.3 % (11 patients) with emergent event including 9 events not related. No safety issue identified.
Literature findings	Natural melatonin was shown to reduce blood pressure and also melatonin agonists may influence the cardiovascular and metabolic system by binding to melatonin receptors and serotonin receptors in the case of Agomelatine. (Dominguez-Rodriguez, 2012 ; Paulis, 2012)
Discussion	Post-marketing data: - 81 cases (moderate incidence 10.6/100 000 PY) - 79% of patients had a relevant context, medical history or concomitant medication that could explain blood pressure increased. - A large number of cases were poorly documented: 43 % of cases did not present any blood pressure values and 75 % of cases did not have baseline values. - Out of the 81 cases, only 9 had a systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHg associated with a difference with baseline values > 20 mmHg (for systolic pressure) and > 10 mmHg (for diastolic pressure). - 4 cases with imputability assessed as likely, 3 were poorly documented and one patient presented a moderate systolic increase (Δ=10 mmHg). - No case with imputability assessed as possible. - Favourable evolution in 90% of cases with documented outcome. Clinical trial data: - No significant between-group difference in IAS 2012 Other sources: - Literature rather showed anti-hypertensive effects of agonist melatoninergic - No safety concern arose from PASS and non-clinical data - No data found from epidemiological data - No pharmacological/biological plausibility found.
Conclusion	False signal

PRAC comments:

The total number of cases were 87 (6 cases reported after the analysis was performed). The

cumulative incidence since grant of MA had increased since the last PSUR (5) period (from 8.4/100 000 PY to 10.6/100 000 PY).

Positive rechallenge was reported in four cases. 31% had hypertension in their medical history.

The PRAC agrees with the MAH's conclusion that many cases are poorly documented. According to the MAH 43% of the cases did not present any blood pressure values, and 75% of cases did not have base line values.

No significant difference in incidence of increased blood pressure was seen between agomelatine and placebo in pooled clinical data (IAS 2012).However, data indicateed a trend that the incidence was higher in the agomelatine group.

The PRAC considered that increased blood pressure should no longer be under close monitoring.

Bilirubin increased

The MAH was requested to pay special attention to cases of bilirubin > 2ULN concomitant with ALAT and/or ASAT > 3ULN, because such cases may predict serious drug-induced liver injuries.

In PSUR 6, the MAH did not presented any analysis of bilirubin increase, but listed blood bilirubin increase as a closed signal.

PRAC comments:

The MAH presented cases with bilirubin > 2 ULN with concomitant increase > 3 ULN of ASAT/ALAT together with the data on hepatotoxicity in the PSUR. Additionally, as jaundice was listed in the SmPC, it was not considered necessary to submit any further data as requested in PAC PSU 011.1. Additionally, as bilirubin increased was considered to fall within the category of hepatotoxicity, which was an important identified risk, it was no longer considered necessary to keep bilirubin increased under close monitoring.

MAH's discussion on the following events under close monitoring:

Following evaluation of PSUR (5) the MAH was asked to discuss the following events in the next PSUR (6):

Alopecia, palpitations, oedema peripheral, panic attacks, muscle spasm and tremor.

Alopecia

Number of cases since MA	47 (39 HCP) (6.5 / 100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 5/47 Within 1 month: 22/47 > 1 month: 12/47 Unknown: 8/47
Class effect	Unknown
Biological/Pharmacological plausibility	No pharmacological plausibility. No alopecia with Agomelatine in toxicology studies (in rates and monkeys up to 625 mg/kg and 375mg p.o. respectively)
Causality assessment Dechallenge/Rechallenge	Doubtful: 44/47 Possible: 1/47 Likely: 2/47 Positive dechallenge: 14/47 Positive rechallenge: 2/47

Clinical data	No significant between-group difference in IAS 2012: • OSS: 0.33% Agomelatine *vs.* 0.11% placebo *vs.* 0.38% SSRI *(NS)* • OSS PC DBS: 0.20% Agomelatine 25-50mg: *vs.* 0.13% Placebo vs 0.23 %(SSRI (*p= 0.740*)
Disproportionality analysis	Similar with AGOMELATINE in comparison to all other Servier drugs (0,34 vs 0.30%, respectively)
Post authorization studies / Patient's support programs	CLE-20098-068 (4246 patients treated / average treatment duration: 168 days) 3 patients of patient presented emergent Alopecia. No safety issue identified.
Literature findings	It has been shown that melatonin may have the capacity to move hair follicles out of the resting (telogen) phase into anagen (Slominski, 2005)

PRAC comments:

No alopecia was seen in non-clinical studies.

No significant difference in incidence of alopecia was observed between agomelatine and placebo in IAS 2012.

The PRAC considered that alopecia should no longer remain under close monitoring.

Palpitations

Number of cases since MA	68 (48 HCP cases) (10.2/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	< 3 days: 26/68 Within 1 month: 26/68 > 1 month: 9/68 Unknown: 6/68 2 days after Agomelatine withdrawal: 1/68
Class effect	Unknown
Biological/Pharmacological plausibility	Unknown
Causality assessment Dechallenge/Rechallenge	Doubtful: 65/68 Likely: 3/68 Positive dechallenge: 39/68 Positive rechallenge: 3/68
Alternative explanation	Relevant medical history: 20/68 • Palpitations: 4/68 • Myocardial ischaemia, ECG signs of myocardial ischaemia: 2/68 • Atrial fibrillation: 2/68 • Myocardial infarction/cardiac failure: 2/68 • Cardiovascular problems: 2/68 • Supraventricular tachycardia/Arrhythmia: 2/68
	• Supraventricular extrasystoles: 1/68 • Anxiety/Panic attacks: 14/68 • Agoraphobia: 1/68 Relevant context: 37/68 • Angina pectoris: 3/68 • Circulatory collapse: 1/68 • Myocardial ischaemia: 1/68 • Rhythm disorders: 9/68 • Ventricular / supraventricular extrasystoles: 2/68 • Anxiety related events: 24/68 • Nightmare: 3/68 • Tension: 1/68 • Restlessness: 11/68 Concomitant drugs: 17/68
Serious (Fatal) cases	16/68 (0)
Outcomes	Recovered: 49/68 Recovering: 6/68 Not recovered: 7/68 Unknown: 6/68

AVAILAILITY OF OTHER RELEVANT SOURCES	
Pharmacological / non clinical data	No safety issue identified
Clinical data	Significant between-group difference IAS 2012: OSS: 0.98% Agomelatine *vs.* 0.49% placebo (*p=0.040*) OSS DB PC: 0.74% Agomelatine *vs.* 0.72% placebo (*p=1*)
Post authorization studies / Patient's support programs	CLE-20098-068 (3611 patients treated / average treatment duration: 131 days) 2 patients presented emergent Palpitations No safety issue identified
Literature findings	No relevant reports found
Discussion	Post-marketing data: - 68 cases (moderate incidence 10.2/100 000 PY) - Large number of events with relevant context or medical history (73%) - Three cases with causality assessed as likely. Cases inadequately documented - Favourable outcome in 89% of the cases with documented outcome Clinical trial data: - Significant between-group difference orienting towards a role of Agomelatine in the overall safety set (OSS) but a non significant between-group difference was found for patient who had the same treatment duration (OSS DB PC) Other sources: - No relevant reports in the scientific and medical literature - No safety concern arose from PASS and non-clinical data
Conclusion	False signal

PRAC comments:

The total number of cases were 76 (8 cases reported after the MAH's analysis was performed).

A significantly higher incidence of events was seen for agomelatine compared to placebo based on OSS. However, based on the OSS DB PC, no significant differences were seen. As the last mentioned safety set corresponds to a set of patients with the same treatment duration, this safety set was considered to be the most appropriate.

The PRAC considered that palpitations should no longer be under close monitoring.

Oedema peripheral

Number of cases since MA	32 (28 HCP cases) (4.8/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	After the first intake: 4/32 within 1 week: 6/32 within 1 month: 14/32 > 1 month: 2/32 unknown: 2/32
Causality assessment Dechallenge/Rechallenge	Doubtful: 30/32 Possible: 1/32 Likely: 1/32 Positive dechallenge: 20/32 Positive rechallenge: 1/32

Alternative explanation	Relevant medical history: 13/32 • Oedema peripheral: 2/32 • Peripheral vascular disorder / Venous insufficiency: 2/32 • Allergy: 1/32 • Hypothyroidism: 3/32 • Gout / Rheumatoid arthritis: 2/32 • Obesity: 3/32 Relevant context: 3/32 • Fluid retention 1/32 • Vein disorder: 1/32 • Lymphadenitis: 1/32 Concomitant drugs: 11/32

Serious (Fatal) cases	4/32 (0)
Outcomes of the events	Recovered : 18/32 Recovering : 5/32 Not recovered : 4/32 Unknown : 5/32
Novelty of reaction	Yes

Clinical data	No significant between-group difference in IAS 2012: OSS: 0.51% Agomelatine *vs.* 0.54% placebo (*p=0.858*) OSS DBPC: 0.47% Agomelatine *vs.* 0.59% placebo (*p=0.571*)
Post authorization studies / Patient's support programs	CLE-20098-068 (3611 patients treated / average treatment duration: 131 days) 3 patients presented emergent Oedema peripheral No safety issue identified

PRAC comments:

The total number of events was 40 (eight cases reported after finalization of the analysis).

No significant difference in incidence of oedema peripheral was seen between agomelatine and placebo based on pooled clinical data (IAS 2012).

The PRAC considered that oedema peripheral should no longer be under close monitoring.

Panic attacks

Number of cases since MA	35 (25 HCP) (5 / 100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 12/35 Within 1 month: 9/35 > 1 month: 9/35 Unknown: 5/35
Causality assessment Dechallenge/Rechallenge	Doubtful: 33/35 Possible: 1/35 Likely: 1/35 Positive dechallenge: 24/35 Positive rechallenge: 1/35

Alternative explanation	Relevant medical history: 14/35 • Anxiety/Panic attack: 13/35 • Suicidal ideation: 1/35 • Post-traumatic stress disorder: 1/35 • Burnout syndrome: 1/35 Relevant context: 13/35 • Anxiety: 8/35 • Suicidal ideation: 4/35 • Nightmare: 2/35 • Akathisia: 1/35 • Recent withdrawal of psychoactive drug: 2/35
Serious (Fatal) cases	9/35 (0)
Outcome of the event	Recovered: 29/35 Recovering: 3/35 Not recovered: 1/35 Unknown: 2/35
Clinical data	No significant between-group difference in IAS 2012: OSS: 0.40% Agomelatine *vs.* 0.32% placebo (*p=0.836*) OSS DB PC: 0.27% Agomelatine *vs.* 0.24% placebo (*p=0.802*)
Post authorization studies / Patient's support programs	CLE-20098-068 (3611 patients treated / average treatment duration: 131 days) 6 patients presented emergent Panic attack No safety issue identified

PRAC comments:

The total number of cases were 41 (6 cases reported after finalization of the analysis).

No significant difference in incidence of panic attacks was seen between agomelatine and placebo based on pooled clinical data (IAS 2012).

The PRAC considered that panic attacks should no longer be under close monitoring.

Muscle spasm

Number of cases since MA	36 (28 HCP cases) (4.7/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 16/36 Within 1 month: 10/36 > 1 month: 3/36 Unknown: 6/36 After Agomelatine withdrawal: 1/36
Causality assessment Dechallenge/Rechallenge	Doubtful: 35/36 Likely: 1/36 Positive dechallenge: 21/36 Positive rechallenge: 1/36
Serious (Fatal) cases	8/36 (0)
Outcome of the event	Recovered: 26/36 Recovering: 2/36 Not Recovered: 5/36 Unknown: 3/36

Clinical data	No significant between-group difference in IAS 2012: • OSS: 0.78% Agomelatine vs 0.49% (NS) placebo vs 0.43% SSRI • OSS PC DB : 0.88% Agomelatine 25-50 mg: *vs.* 0.55% Placebo *vs.* 0.57 % SSRI *(p= 0.197)*
Disproportionality analysis	Similar with AGOMELATINE in comparison to all other Servier drugs (0.32 vs 0.40%, respectively)
Post authorization studies / Patient's support programs	CLE-20098-068 (4246 patients treated / average treatment duration: 168 days) 3 patients presented emergent Muscle Spasms. No safety issue identified

PRAC comments:

The total number of cases was 40 (4 cases reported after finalization of the analysis).

No significant difference in incidence of muscle spasm was seen between agomelatine and placebo based on pooled clinical data (IAS 2012).However, it is a trend that the incidence is higher in the agomelatine group.

The PRAC considered that muscle spasm should no longer be under close monitoring.

Tremor

Number of cases since MA	54 (40 HCP) (8/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 27/54 Within 1 month: 11/54 Within 3 months: 4/54 Unknown: 11/54 After Agomelatine withdrawal: 1/54
Causality assessment Dechallenge / Rechallenge	Doubtful: 52/54 Likely: 2/54 Positive dechallenge: 32/54 Positive rechallenge: 2/54
Serious (Fatal) cases	12/54 (0)
Outcome of the events	Recovered: 39/54 Recovering: 4/54 Not recovered: 6/54 Unknown: 5/54
Clinical data	No significant between-group difference in IAS 2012: OSS: 0.63% Agomelatine *vs.* 0.86% placebo (*p=0.271*) OSS DB PC: 0.71% Agomelatine *vs.* 0.76% placebo (*p=0.872*)

PRAC comments:

The total number of reports was 65 (11 cases reported after MAHs analysis).

No significant difference in incidence of tremor was seen between agomelatine and placebo based on pooled clinical data (IAS 2012).

The PRAC considered that tremor should no longer be under close monitoring.

Other unlisted events

In the AR of PSUR 5, the MAH was requested to answer the following questions:

- In the next PSUR a cumulative overview of cases of **thrombocytopenic purpura** should be submitted. The MAH should consider whether there is sufficient evidence that information about this events should be included in the SPC/PIL.

- In the next PSUR a cumulative overview of cases of **possible interactions with warfarin and other anticoagulants** should be submitted. The MAH should consider whether there is sufficient evidence that this event should be informed about in the SPC/PIL.
- In the next PSUR the MAH should provide an overview of the cumulative number of **photosensitivity** reported and discuss causality with agomelatine.

Trombocytopenic purpura

CLINICAL RELEVANCE	
Number of cases since MA	2 (2 HCP cases) (0.4/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	> 1 month: 2/2
Class effect	Unknown
Biological/Pharmacological plausibility	Unknown
Causality assessment Dechallenge/Rechallenge	Doubtful: 2/2 Positive dechallenge: 2/2 Positive rechallenge: 0
Alternative explanation	No
Serious (Fatal) cases	2/2 (0)
Outcome of the event	Recovered: 2/2
AVAILAILITY OF OTHER RELEVANT SOURCES	
Pharmacological / non clinical data	Agomelatine is a non-SSRI, non-SNRI antidepressant. Its lack of effect on monoamine uptake and particularly serotonin explains the fact that, contrary to SSRIs or imipramine-like compounds, Agomelatine is devoid of serotonergic effect, and has no influence on the extracellular levels of serotonin. Thus, an effect of Agomelatine on platelets function, either through SSRI-like mechanism, or through 5-HT2B and 5-HT2C antagonism activity is unlikely and consequently no specific preclinical study has been performed on this aim.
Clinical data	No significant between-group difference in IAS 2012: OSS: 0.10% Agomelatine 25-50 mg *vs.* 0.11% placebo *vs.* 0.05% SSRI *vs.* 0.38% SNRI.
Disproportionality analysis	Lower with AGOMELATINE in comparison to all other Servier drugs (0.02 vs 0.07%, respectively)
Post authorization studies / Patient's support programs	No case
Literature findings	No relevant reports found

Discussion	Post-marketing data: - 2 cases (very low 0.4/100 000 PY) - No case with imputability assessed as possible or likely Clinical trial data: - No significant between-group difference in IAS 2012 Other sources: - No relevant reports found in the literature - No safety concern arose from PASS and non-clinical data - No data found from epidemiological data - No pharmacological/biological plausibility found.
Conclusion	False signal

PRAC comments:

The MAH informed about two cases with positive dechallenge. No narratives were provided. Overall, the evidence was not considered sufficient to conclude on an association between agomelatine and thrombocytopenic purpura.

The MAH was requested to keep thrombocytopenic purpura under close monitoring.

Drug interaction with anticoagulants

Number of cases since MA	9 (all HCP cases) (2.4/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 to 2 weeks: 8/9 Unknown: 1/9
Causality assessment Dechallenge/Rechallenge	Doubtful: 9/9 Positive dechallenge: 4/9 No positive rechallenge
Alternative explanation	Relevant context: 3/9 • Inflamation, Gastroenteritis: 2/9 • Concomitant introduction on the same day of Agomelatine and anticoagulant drug: 1/9 Concomitant drugs: 4/9 • Allopurinol, Statines, Cefixime
Serious (Fatal) cases	5/9 (0)
Outcome of the event	Recovered: 7/9 Unknown: 2/9
Clinical data	No case identified
Post authorization studies / Patient's support programs	Not performed

Pharmacological / non clinical data	No safety issue identified
Clinical data	No case identified
Post authorization studies / Patient's support programs	Not performed
Literature findings	No relevant reports found
Discussion	Post-marketing data: Overall, 9 cases were identified, amongst them: - A drug interaction was clearly suspected by the reporter in 4 cases. - In 4 cases, one or more concomitant treatments were reported and were known to increase oral anticoagulant effect (Allopurinol, Statines, Cefixime) - The reported events (all HCP) were: • INR increased in 6 cases (1 case with phenprocoumon, 3 cases with fluindion including 2 cases with concomitant hematuria and 2 cases with warfarine). • INR abnormal in 2 cases (both with phenprocoumon) • Prothrombin time prolonged and activated partial thromboplastin time prolonged in 1 case with warfarine. Clinical trial data: - No case was identified Other sources: - No relevant reports found in the literature - No pharmacological/biological plausibility found.

PRAC comments:

No narratives were submitted, making it impossible to evaluate these cases. However, the committee was aware of a serious case of interaction between agomelatine and warfarin, with an increased INR three days after agomelatine introduction (F/42 years old). It was not clear whether this case was included in the MAH's database.

It was recommended that narratives be provided to investigate this highly important issue.

Drug interactions with anticoagulants should be held under close monitoring.

Photosensitivity

Number of cases since MA	16 (15 HCP cases) (2.1/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 5/16 Within 1 month: 6/16 > 1 month: 4/16 Unknown: 1/16
Causality assessment Dechallenge/Rechallenge	Doubtful: 16/16 Positive dechallenge: 6/16 No positive rechallenge
Serious (Fatal) cases	2/16 (0)
Outcome of the event	Recovered: 10/16 Recovering: 2/16 Not recovered: 3/16 Unknown: 1/16

Clinical data	No significant between-group difference in IAS 2012: OSS: 0.05 % Agomelatine 25-50 mg *vs.* 0% Placebo
Disproportionality analysis	Similar with Agomelatine in comparison to all other Servier drugs (0.14 vs 0.09%, respectively)
Post authorization studies / Patient's support programs	No safety issue identified
Alternative explanation	Relevant medical history: 3/16 • Photosensitivity: 2/16 • Food allergy: 1/16 Relevant context: 2/16 • Important sun exposure: 2/16 Concomitant drugs: 5/16

PRAC comments:

Information on the case reports was insufficient. In addition, it was not possible to draw any conclusion regarding causality with agomelatine from the IAS.

For the period from the last PSUR only two cases of photosensitivity were reported. The majority of the reported events were classified as non-serious. Consequently, the PRAC considered that photosensitivity should no longer be under close monitoring.

Restless leg syndrome

Restless leg syndrome has been generated as a signal in the MAH's database in this PSUR period:

CLINICAL RELEVANCE	Urticaria
Number of cases since MA	29 patients (27 HCP) (3.4/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 day: 9/29 Within 1 week: 4/29 Within 1 month: 7/29 > 1 month: 3/29 Unknown: 6/29
Class effect	Unknown
Biological/Pharmacological plausibility	Unknown
Causality assessment Dechallenge/rechallange	Likely: 1/29 Doubtful : 28/29 Positivive dechallenge: 14/29 Positive rechallenge: 1/29
Alternative explanation	Relevant medical history: 8/29 • Restless legs syndrome Relevant medical context : 3/29 • Somatoform disorder: 1/29 • Restlessness / Agitation: 2/29 Concomitant drugs: 7/29 • Quetiapine: 1/29 • BZD withdrawal: 2/29 • SSRI / antidepressant switch: 4/29
Serious ICSR (Fatal)	1/29 (0)
Outcome of events	Recovered: 16/29 Recovering: 3/29 Not recovered: 5/29 Unknown: 5/29

AVAILAILITY OF OTHER RELEVANT SOURCES	
Pharmacological / non clinical data	No safety issue identified
Clinical data	Significant between-group difference in : IAS (Agomelatine 25-50 mg: 0.39% vs. placebo: 0.05%) (p-value = 0.022) OSS PC DBS (Agomélatine 25-50 mg 0.30% vs. placebo 0.04%) (p-value = 0.05) Higher incidences in Agomelatine group were also found in OSS PC DBS set and a trend is also observed in patients with no previous antidepressant drugs.
Disproportionality analysis	Higher with Agomelatine in comparison to all other Servier drugs (0,21% vs 0.03%, respectively)
Post authorization studies / Patient's support programs	CLE-20098-068 (4246 patients treated / average treatment duration: 168 days) 5 events "restless legs syndrome" were reported (0.1 %). 3 of them were considered as related to treatment by the investigator and 1 event led to treatment discontinuation. No event was serious or fatal. No safety issue identified.
Epidemiological data	Prevalence largely varies according to RLS definition: Health survey in a 57-years-old Finnish urban population (Juuti 2010): from 13 to 20% in women, from 10 to 15% in men; strong association with depression and anti-depressant treatment.
Literature findings	No data found associated to Agomelatine. Adverse effect already described with Paroxetine. Unclear relation between RLS and Parkinson's Disease (Verbaan 2010, Moller 2010).
Discussion	Post-marketing data: - Overall frequency 3.4/100 000 PY - 45% of patients did not present with a relevant context or medical history likely to induce or favour Restless legs syndrome. - No case with imputability assessed as possible. - One isolated case with imputability assessed as likely and 6 cases occurring within 24h - RLS was the only term reported in 35 % of the patient-cases (10/29). - Disproportionality analysis showed a higher incidence of RLS wih Agomelatine than with other Servier drugs. Clinical trial data: - A significant trend for more events in the Agomelatine group was observed. Other sources: - No relevant reports found in the literature - No safety concern arose from PASS and non-clinical data - No data found in literature or from epidemiological data. - No pharmacological/biological plausibility found.
Conclusion Action taken	Addition of Restless legs syndrome to section 4.8 of the SmPC and update of the package leaflet.

Based on the above analysis and taking into account the higher prevalence of RLS with Agomelatine than with other Servier drugs and the significant difference between all clinical studies sets, restless legs syndrome was identified as a new non important risk. In this respect, the MAH commits to submitting amendment of the SPC to add restless legs syndrome in the section 4.8 "Undesirable effects" within 2 months upon receipt of the CHMP assessment of the PSUR.

PRAC comments:

A significant difference in incidence between the agomelatine group and the placebo group in both IAS and OSS PC DBS was found. The PRAC supported the MAH's conclusion on the RLS, and a SPC update to include restless leg syndrome as an ADR in section 4.8 within this PSUR procedure was endorsed.

Evaluation of risks and new information

The following events were under close monitoring in the PSUR period:

Confusion, tinnitus, pancreatitis, hyponatraemia/SIADH, convulsion, blood bilirubin increased, muscular events and blood pressure increased, urticaria, alopecia, palpitations, oedema peripheral, panic attacks, muscle spasm and tremor.

Urticaria had been included in section 4.8 of the SPC in the context of angioedema being generated as a signal in the EV database.

For the other events, the MAH performed comprehensive signal evaluations.

Based on the review of these data, and with emphasis on the Integrated Analysis of Safety (IAS), the PRAC considered that the following events should no longer be under close monitoring:

Confusion, myalgia, blood pressure increased, blood bilirubin increased, alopecia, palpitations, oedema peripheral, panic attacks, muscle spasm and tremor.

For the events **tinnitus** and **convulsions**, the PRAC considered that evidence was sufficient for these events to be included in section 4.8 of the SmPC with a respective update of the package leaflet to follow.

The PRAC considered that there was some evidence indicating that agomelatine could induce hyponatraemia. However, this needed to be elucidated in more detail. The MAH was asked to submit narratives of cases that had previously not been submitted, including narratives of the latest reported cases.

Pancreatitis should remain under close monitoring.

Additionally, **thrombocytopenic purpura** and **drug interactions with anticoagulants** should be included as events under close monitoring.

Restless leg syndrome was generated as a signal in the MAH's database. The PRAC recommended that restless leg syndrome be added in section 4.8 of the SmPC with a respective update of the package leaflet to follow.

Restless leg syndrome, tinnitus and convulsions should be classified in the category "other risk".

Characterisation of risks

Important identified risk - Hepatotoxicity

Evaluation of post-marketing data from PSUR 6:

Overall, 12 cases of severe hepatic dysfunction (hepatic failure or cases not reported as hepatic failure, but with evocative signs and symptoms of severe hepatic dysfunction such as encephalopathy, coagulation disorders) were received cumulatively. Eight (8) of these cases had been assessed by the CHMP during the assessment of PSUR 5 and the type II variation submitted following the conclusions of PSUR 5. The remaining 4 cases were presented by the MAH in PSUR 6:

S1201****In this case, a 90 year old woman with moderate overweight and a past medical history of hypertension, prinzmetal's angina, polyarthrosis and retinal ablation. The patient also had a recent history of GI bleeding following intake of NSAIDs (with abnormal clotting, INR 1.5, protrhombin time 51 %) and worsening of the general condition. Agomelatine was started at 25 mg daily. The patient used concomitant medications such as NSAIDs, hydrochlorothiazide, torasemide, oxazepam, pantoprazole, metoprolol, melperone and ramipril. Approximately one month after first intake of agomelatine there was a increase of ALT to 19 ULN, AST to 7.5 ULN, GGT 12 ULN and a concomitant increase in leucocytes count to 14 300 , CRP to 6.2 and a decrease in natreamia to 128. Prothrombin time was 48 %. Agomelatine was stopped and transaminase level rapidly improved; 3 days after last intake of agomelatine ALT was 10.5 ULN and AST 1.7 ULN. 4 days later the patient died. The MAH considers that a lot of confounding factors could be incriminated, more likely than Agomelatine to be responsible for liver enzyme disturbances such as numerous concomitant treatments, hyponatremia suggesting hydro-electric disturbances, cardiovascular events with ischemic liver. The death is not related to liver failure (no bilirubin elevation) but more probably to the general and cardiovascular condition. The MAH has assessed the case as possibly related to agomelatine.

S1300****:

This case concerns a male patient between 50 and 60 years old. The patient had a medical history of depression and chronic alcohol intake for many years. He has been treated since an unspecified date in 2011 with agomelatine (dose unspecified) for depression. No information on previous or concomitant medication, if any. No information on liver function tests at baseline, if performed. On an unspecified date (possibly in the end of 2011), lab tests showed increased liver enzymes (Increased transaminases, not "very high" according to the reporter). Agomelatine was stopped after one or two months of treatment. The patient was admitted to hospital one week later for suspicion of liver failure due to alcoholic cirrhosis (previously not diagnosed). He presented with coagulopathy (increase of Prothrombin time, no information on Factor V). No information on clinical signs (including icterus). The patient was transferred from the Geriatric Unit to the Gastroenterology Unit, where he eventually died a few days later. No liver biopsy was performed. No autopsy was performed. No further information was available. Outcome: Fatal. According to the reporter, the transaminase increase was related to the alcoholic cirrhosis. In a follow up information the reporter was eventually not sure that the patient died. The MAH has assessed this case as not assessable.

S1300****:

This case concerns a 42 year old female patient with an unspecified medical history treated with agomelatine 25 mg daily for an unspecified indication. One week after initiation of treatment, the patient was hospitalized for massive paracetamole intake with suicidal intention. AST was 6646 IU/L and ALT 4890 IU/L. The patient was jaundiced with impaired consciousness and INR of 6.28.

Fatal outcome occurred 8 days after the patient was admitted to hospital. The MAH has assessed the case as not related to agomelatine.

S1300****

This case concerns a 45 year female patient with medical history if obesity, sleeve gastrectomy followed by gastric by-pass, alcoholism and chronic hepatitis B infection treated with entecavir. HBV replication was reported to be well controlled. She has been treated since an unspecified date with VALDOXAN (dose and indication were not specified). Concomitant treatment included Entecavir for hepatitis B. No information on previous medication, if any. No information on baseline lab tests, if performed. In FEB-2013, three to four months after Valdoxan initiation, the patient was hospitalized for encephalopathy, confusion, AST increase (800-1000 IU/L), slight ALT increase (around 100 IU/L), Prothrombin level 28%, ALP increase and GGT increase. Lab tests showed no paracetamol in blood. No information regarding viral serologies, except negative hepatitis B viral load. The patient was treated with Lactulose, with positive effect on encephalopathy. As lab tests then showed worsening of Prothrombin level decrease and AST increase, the patient was transferred to the intensive care unit. Rhabdomyolysis was diagnosed (with severe CPK increase). The patient presented with hepatic insufficiency, pneumopathy and multiorgan insufficiency. Liver biopsy showed deterioration of liver, with severe hepatic fibrosis. The patient eventually died on 06-FEB-2013 in a context of cardiovascular failure and multiorgan insufficiency. No further information available. Fatal outcome. According to the GP, liver function tests were prescribed and performed (no other informations).

The MAH assessed the case as follows:

Serum bilirubin is unavailable, but we are told she had conjunctival icterus (i.e. jaundice). Taken together, the normal ALT, elevated AST and high AST:ALT ratio with jaundice, low serum albumin and prolonged prothrombin time suggests to us that she has alcoholic hepatitis possibly with disseminated intravascular coagulation. The later liver histology which showed steatohepatitis is consistent with this diagnosis. The patient was transferred to another department at the university hospital due to liver and respiratory failure developing severe bilateral pneumonia: criteria for ARDS are well documented clinically, and by laboratory and CT scan findings.

At initial hospital admission the aminotransferase were normal or only moderately increased for AST (probably 2-3xULN) while features for marked liver dysfunction were present (prothrombin and factor V levels below 30% of normal). The PT level may also be decreased in patients with disseminated intravascular coagulation. CT scan reportedly showed enlarged fatty liver without evidence for portal hypertension. Necropsy a few days later apparently showed steatohepatitis with portal and sinusoidal fibrosis.

These findings indicate that severe liver disease was present when the patient developed pneumonia. The features are characteristic for alcoholic liver disease [moderately increased aminotransferase (AST>ALT)] potentiated by obesity. The fact that the patient had stopped taking alcohol 3-4 weeks earlier does not rule out this diagnosis, particularly in the context of obesity. Although chronic hepatics B might have participated in causing fibrosis, the description of the lesions found at necropsy suggests that viral replication was actually well controlled, as otherwise indicated by undetectable HBV DNA in serum. The low level of ALT is unusual for an agomelatine-induced liver injury.

Thereafter, the patient developed circulatory failure combined with anemia (hemoglobin level 5.7 mmol/L) and respiratory failure. The development of severe hypotension and hypoxemia secondary to ARDS and anemia fully explains the subsequent marked increase in serum aminotransferase levels due to ischemic (or hypoxic) hepatitis as well as multiorgan failure and death. Hypoxic hepatitis has been well documented by post mortem findings in the liver. What is not completely

clear is whether bacterial infection was responsible for bilateral pneumonia. Bacterial infection is extremely common in patients with severe alcoholic hepatitis. Although the responsibility of agomelatine, as aggravating factor cannot be ruled out, its responsibility would be unlikely.

The MAH concluded that the case was unlikely related to agomelatine.

PRAC comments:

The PRAC considered that one case had a temporal relationship between agomelatine and the observed increase in transaminases. However, due to the serious underlying diseases and several concomitant treatments, causality with agomelatine could not be established. In another case it was agreed with the MAH that the case report did not include enough information to assess causality, whereas in a third case the observed event of liver failure was likely due to paracetamol overdose and not related to agomelatine. In the last case the history of alcohol abuse and hepatitis B precluded the assessment of causality with agomelatine. The AST/ALT-ratio of more than 2:1 may be suggestive of alcoholic injury. However, a possible role of agomelatine as having an additive effect, could not be ruled out, due to the observed temporal relationship.

Overall, the 4 cases of severe hepatic dysfunction received during the reporting period and not previously assessed by the CHMP, included several confounding factors making it difficult to evaluate the causality with agomelatine. It was concluded that these cases were not considered to add any new knowledge with regards to the hepatotoxic potential of agomelatine.

During the reporting period of PSUR 6, 57 cases were received reported as hepatitis or with a transamine increase > 10 ULN and/or transaminase increase > 3 ULN, with concomitant bilirubin increase > 2 ULN. In these cases the daily dosage of agomelatine was 25 mg in 29 of the cases (51%), 50 mg in 20 cases (35%), 75 mg in 1 case and not specified in the remaining 7 cases. 28 of the patients had a medical history of alcoholism and/or obesity/overweight and/or transaminase increase and/or another risk factor for non-alcoholic steatohepatitis (NASH), such as hypertension, hypercholesterolemia or diabetes mellitus. In 5 of the cases (9%) agomelatine was taken concomitantly with medicinal products associated with risk of hepatic injury.

The time to onset of these cases was from 1 day to 22 months, with 19 (33 %) of the events occurring between 6 and 12 weeks after agomelatine initiation.

According to the MAH's evaluation, in 10 of the 57 cases (18 %) the SmPC guidance was not adequately followed as agomelatine was not immediately stopped despite the occurrence of biological and/or clinical signs of potential liver injury. According to the MAH the outcome was favourable in 24 cases (16 patients recovered, 8 patients recovering), were the SmPC guideline was followed.

The MAH's group of experts, the Liver Safety Committee considered that 1 case was not assessable, 2 cases not related to agomelatine, in 3 cases agomelatines role was assessed as probable, and in 19 as possible. The remaining 23 cases have not yet been evaluated by the MAH's expert group.

PRAC comments:

The serious hepatotoxic reactions presented in these reports caused concern. However, as such reactions have been known to occur with agomelatine, they were not considered to add any new information on the safety profile of agomelatine. In the previous PSUR period (PSUR 5), there were 45 cases of hepatitis, transaminases > 10 ULN and/or transaminases > 3 ULN with concomitant bilirubin increase > 2 ULN. The number of reports in PSUR 6 was slightly higher with 57 cases, however this could be explained by higher exposure to agomelatine in the period of PSUR 6, along with increased attention on reporting following the dissemination of the DHPC and updated educational material towards the end of 2012. As the data lock point for PSUR 6 was 19.02.2013,

only 4 months after the dissemination of the DHPC and updated educational material, the risk minimisation measures were not expected to had had any major impact on reducing the number of serious hepatotoxic reactions or improving compliance with the SmPC at the time of DLP of PSUR 6.

It was noted that the adherence to the SmPC guideline was associated with a favourable outcome in 66 % of these cases. This emphasizes the importance of strictly complying with the guidance in the SmPC. In its assessment of cases of non-compliance with the SmPC, the MAH has focused on cases were recommendations in section 4.4 to immediately stop treatment with agomelatine following occurrence of biological and/or clinical signs of potential liver injury were not followed. However, there was no analysis of whether liver function tests has been performed according the guidance of the SmPC. Early detection of potential liver injury is also of outmost importance to reduce the severity of hepatotoxic reactions. When analyzing the effect of risk minimisation and compliance to the SmPC in future reports, the MAH was advised to include an analysis of whether liver function tests have been performed according to the SmPC.

Additionally, the MAH was asked in the Assessment Report for the previous PSUR (PSUR 5) to provide follow up information about 6 cases of hepatitis that were not evaluated in PSUR 5 due to lack of documentation. Of these 6 cases, 1 poorly documented case has not yet been evaluated by the MAH's expert committee. 3 poorly documented cases were considered closed as the reporters refused to provide additional information. These cases were evaluated as not assessable. The remaining 2 cases were evaluated as possible related to agomelatine in one case, and unlikely related in the last case. Overall, the MAH considered that these cases did not have any impact on the overall conclusion of the last PSUR.

PRAC comments:

It was agreed that these cases did not impact the overall conclusion of the last PSUR. Hepatitis is listed as an adverse event in the SmPC of agomelatine.

In addition to the cases presented in the above categories, there were 69 cases of transaminases > 3 ULN reported in the period covered by PSUR 6. This is similar to the reporting in the previous PSUR (PSUR 5), were 77 cases of transaminases increased > 3 ULN was reported. The MAH's analysis of the cases from PSUR 6 showed that in 15 of these 69 cases the SmPC guideline to discontinue agomelatine was not followed, whereas of the 38 cases were the SmPC guidance was followed, 26 cases had a favourable outcome.

PRAC comments:

As with the more severe reactions presented above, these cases emphasized the importance of adherence to the SmPC guideline. Overall, the reporting of increased transaminases > 3 ULN was similar to the incidence in previous PSURs, thus no new information on the safety profile of agomelatine was identified from these reports.

In the Final Assessment Report to PSUR 5, the MAH was asked to provide follow up information of 36 cases of ASAT/ALAT > 3 ULN that were not evaluated in PSUR 5 due to lack of documentation. Of these 36 cases 4 poorly documented cases were not submitted to the MAH at the time of data lock point of PSUR 6. 6 cases were considered closed as the reporters refused to provide additional information. These cases were evaluated as not assessable. In the remaining 26 cases, the role of agomelatine was assessed as probable in 4 cases, possible in 11 cases, unlikely in 9 cases and 2 cases were assessed as not related to agomelatine. The MAH considers that these cases did not change the overall conclusion of PSUR 5 a conclusion that was supported by the PRAC.

An increase was seen in the reporting of cases of transaminases ≤ 3 ULN of 49 % from 15.2/100 000 patient years in the previous PSUR to 22.6/100 000 patient year in the period covered by this

PSUR. This could be explained by the increased attention to reporting of hepatic adverse events following the dissemination of the DHPC in October 2012.

Overall, the incidence of liver adverse events was 79.6/100 000 patient years in the period covered by PSUR 6, an increase from the 62.4 / 100 000 patient years reported with the previous PSUR 5. According to the MAH, the overall increase in cases with liver adverse events could be explained by the 49 % increase of incidence of cases with transaminases ≤ 3 ULN.

PRAC comments:

Although the incidence of liver adverse events was slightly increased from the previous PSUR, it should be noted that the incidence reported within this period was lower than the incidence reported within the PSUR preceding PSUR 5, with a incidence of 79.6/100 000 patient years in PSUR 6 compared to 83.4/100 000 patient years in PSUR 4.

Overall no new findings with regards to hepatotoxicity were identified from the data presented in this PSUR. The reported events were similar in frequency and severity compared to previous PSURs. The reports of severe hepatotoxic reactions were of concern, but it was considered too early to evaluate the effect of the risk minimisation measures implemented following the conclusion of the previous PSUR (PSUR 5).

Cumulative review

Based on the updated overall agomelatine clinical trials database, an increased incidence (1. 75 %) of transaminase elevations (> 3 ULN) has been observed after administration of agomelatine 25/50 mg (1.34 % at 25 mg/d and 2.51 % at 50 mg/d) as compared to placebo (0.50 %). In clinical trials, hepatic reactions observed on Agomelatine usually consist in asymptomatic isolated transaminases elevation in majority of patients, detectable within the first months of treatment and reversible after drug cessation or on treatment. When considering the patients for which a follow-up was available on treatment, 52% of the patients who reported a transaminase elevation > 3ULN recovered under Agomelatine maintained treatment. No severe hepatic dysfunction has been reported in clinical studies.

In post-marketing surveillance, 746 cases of Liver adverse reactions have been received since Market Authorisation, including 12 cases of severe hepatic dysfunction. The incidence of reported cases is stable since 2010, with the incidence of liver adverse events varying from 107.6/100 000 patient years in PSUR 2 to 62.4/100 000 patient years in PSUR 5. In the 335 cases of transaminase increase > 3 ULN, hepatitis and/or severe hepatic dysfunction received since Market Authorisation, the role of Agomelatine was assessed by the Liver Safety Committee as probable in 38 cases (11.3%), possible in 107 cases (31.9%) and unlikely in 46 cases (13.7%). Twenty-one (21) cases were considered as not related to Agomelatine (6.3%), and 29 cases were considered as not assessable (8.7%). One case was not evaluated as there was no transaminase increase (0.3%). The remaining 93 cases (27.8%) were not yet evaluated at the time of this report.

Out of the 335 patients, 244 (72.8%) were female. The ratio of female patients is slightly higher than in the global population of patients who presented with adverse reactions under Agomelatine treatment (64.6% of female). However, the gender was not specified in 4.5% of the cases of the global population, which constitutes a bias in the analysis. Taken into account all 746 cases of Liver adverse reactions, the ratio of female patients is comparable with the global population: 479 patients out of 746 were female (64.2%, gender being not specified in 4.4% of the cases). In conclusion, female patients do not seem to be at higher risk of hepatic adverse reaction.

In 34.1% of the patients who presented with hepatitis or liver failure, a Non-Alcoholic SteatoHepatitis (or risk factors for NASH) was reported in medical history, which is slightly less

than in the population with isolated transaminase increase > 3 ULN (37.8%). NASH or risk factors for NASH do not seem to be a risk factor for more severe hepatic adverse reactions.

In 5.6% of the patients who presented with hepatitis or liver failure, baseline lab tests showed elevated transaminases, which is less than in the population with isolated transaminase increase > 3 ULN (13.4%). An abnormal baseline lab test does not seem to be a risk factor for more severe hepatic adverse reactions. No risk factor was identified from post-marketing surveillance.

MAH's conclusion: In clinical trials, hepatic reactions observed on Agomelatine usually consist in asymptomatic isolated transaminases elevation in majority of patients, detectable within the first months of treatment and reversible on treatment or after drug cessation. No severe hepatic dysfunction in clinical studies has been reported. The mechanism of potential liver adverse reactions still appears to be usually cytolytic.

There is neither evidence of cholestatic nor of associated hypersensitivity reactions. An idiosyncratic mechanism is the most probable.

Cases of liver injury, including hepatic failure, 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 surveillance, but no risk factor was identified. Since cases of severe liver dysfunction have been reported, risk minimization measures (SPC updates, updated physician's guide distribution and DHPC dissemination) have been implemented in 2012.

In view of the above data, the MAH considered that the additional risk minimization measures proposed are appropriate to contribute to the optimization of benefit/risk for Agomelatine in the interest of the patient.

Hepatotoxic reactions remain under close monitoring.

PRAC comments:

Overall, it was considered that the cumulative review of the identified risk of hepatotoxicity did not reveal any new information. The frequency of increased transaminases > 3 ULN is in accordance with the number stated in the SmPC. The reporting of liver adverse events from post marketing is stable, and comparable to the finding in previous PSUR intervals.

In the conclusion of the Final Assessment Report of PSUR 5, the MAH was asked to report any association between slightly elevated ASAT/ALAT pre-treatment and more severe elevation later during treatment or post-treatment. The MAH concluded that there was no such association based on the fact that 5.6 % of the patients who presented with hepatic failure or hepatitis had elevated transaminases at baseline, compared to the population with isolated transaminases increase > 3 ULN where the number was 13.6 %. The position of the MAH that there did not seem to be any clear association based on these data, was endorsed. However, due to the relatively low number of cases in the category with the most severe hepatic reactions, it was difficult to draw any firm conclusions. The MAH was advised to continue in future PSURs to analyse the reports to elucidate if there were any risk factors for the development of the more severe hepatoxic reactions.

The MAH was also asked to discuss if reports of elevated ASAT/ALAT were associated with NASH (non-alcoholic steatohepatitis) or any of the risk factors for NASH such as hypertension, obesity, diabetes type II and metabolic syndrome. The MAH concluded that there was no association with NASH or risk factors for NASH and the most severe hepatic adverse events of hepatitis and hepatic failure. Among the patients presenting with hepatitis or hepatic failure, 34.1 % had NASH or risk factors for NASH, compared to 37,8 % of patients with isolated increases in transaminases > 3 ULN. Again, the PRAC agreed that these data did not indicate any association between NASH or risk factors of NASH, and the more severe hepatic adverse events, but no firm conclusion could be drawn due to the relative low number of cases in the category with more severe events.

Additionally, the MAH was asked to calculate the incidence of hepatic adverse events in women and compare this with the incidence of such events in men. The MAH concluded that female patients do not seem to be at higher risk of hepatic adverse events. The PRAC agreed with this assessment, as the MAH's analysis showed that of the 746 liver adverse events, the ratio of female patients was 64.2 %, compared to 64. 6 % ratio of female patients for all adverse events. Thus, there did not seem to be any indication that females were at higher risk of hepatic adverse events.

Important identified risk – Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)

During the 48-month period of post-marketing surveillance, 5 cases of drug interaction with potent CYP 1A2 inhibitors (1 non-HCP) were reported, which corresponds to an estimated incidence of 0.6 / 100 000 patient years. Out of the 5 cases, 2 were assessed as serious.

The outcome was recovered in 4 cases and unknown in 1 case. These cases did not provide any new safety insight to Agomelatine safety.

The MAH concluded that interaction with potent CYP 1A2 inhibitors should be maintained as important identified risk and listed as contraindication and continue to be closely monitored.

PRAC comments:

The MAH's conclusion was supported by the PRAC. No new information regarding this important identified risk was identified from this cumulative review. Interactions with potent CYP 1A2 inhibitors should continue to be closely monitored, and listed in the RMP as an important identified risk.

Important potential risk- Suicide

Frequency with 95 % CI

1/ Clinical trials

Incidence rate of suicidality based on EAE in the TME "Suicide/self-injury" during treatment or within the month following discontinuation of study treatment in the MDD safety set

		Agomelatine 25/50 mg	Placebo
N		7519	1393
All	n (%)	111 (1.5)	23 (1.7)
	pm	0.30	0.50
Suicide attempt		48 (0.6)	11 (0.8)
Suicidal ideation		30 (0.4)	7 (0.5)
Intentional overdose		16 (0.2)	-
Depression suicidal		6 (0.1)	3 (0.2)
Completed suicide		4 (0.1)	1 (0.1)
Intentional self-injury		4 (0.1)	1 (0.1)
Suicidal behaviour		3 (0.04)	-
Self injurious behaviour		1 (0.01)	-

pm: number of patients per 100 patients-months

In Agomelatine phase III trials, no increased risk of suicidality in patients treated with Agomelatine has been observed (including in patients aged 18-30 years).

2/ Post-marketing surveillance

During the post-marketing experience, 456 Suicide events were reported in 366 patients, representing an estimated incidence of 42.7 for 100 000 patients-year, not taking into account 109 non-serious cases of post-authorisation studies.
Among them, 33 cases of intentional overdose or intentional multiple drug overdose without concomitant suicide events were not taken into account in the following analysis.
Regarding the remaining 333 patients, the number of events (335 events) is summarized below:

Number of suicidal events since Market Authorization

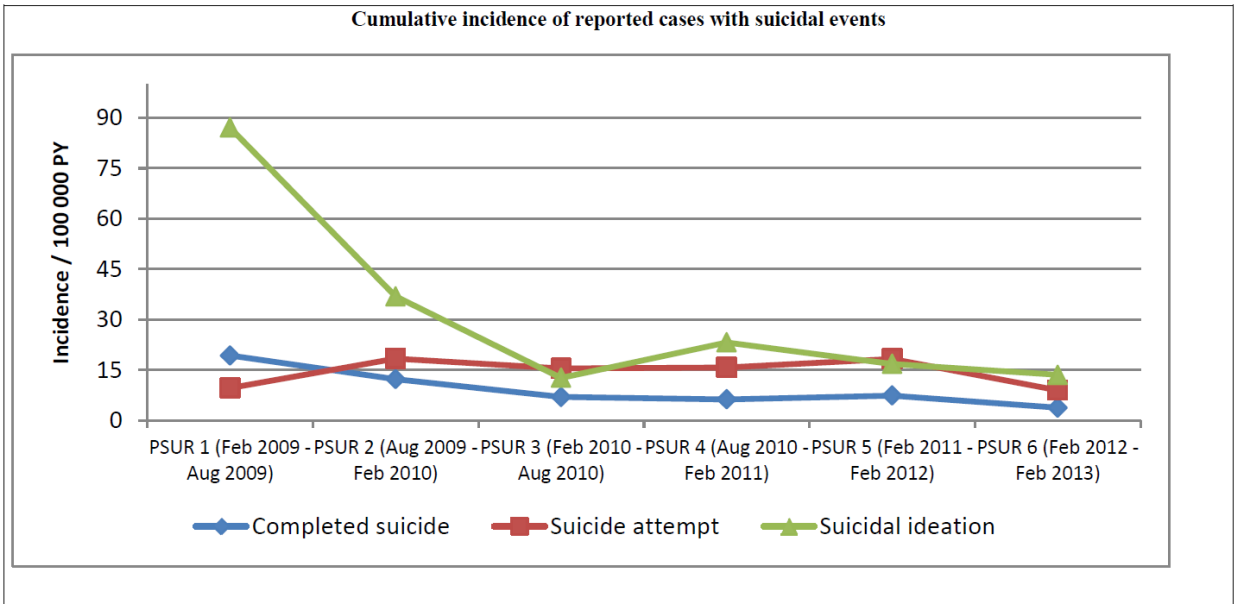
ADR Term	Number of events (serious event)
Completed suicide*	52 (52)
Depression suicidal	1 (1)
Intentional self-injury	10 (9)
Suicidal behaviour*	5 (4)
Suicidal ideation*	149 (94)
Suicide attempt*	118 (118)
Total of events	335 (278)

**Listed events*

The 14 cases (16 events) of Depression suicidal, Intentional self-injury and Suicidal behavior are not taken into account in the following analysis of incidence.

Incidence of reported cases of Suicidal events since Market Authorization

PSUR period	N events	Patients-months	Interval reported incidence (/100 000 patients-years)	Cumulative reported incidence
Completed suicides				
Feb 09 / Aug 09	2	124 276	19.3	
Aug 09 / Feb 10	4	390 368	12.3	14
Feb 10 / Aug 10	5	853 140	7.0	9.7
Aug 10 / Feb 11	6	1 137 021	6.3	8.1
Feb 11 / Feb 12	21	3 402 842	7.4	7.7
Feb 12 / Feb 13	14	4 415 694	3.8	6.1
Suicide attempts				
Feb 09 / Aug 09	1	124 276	9.7	
Aug 09 / Feb 10	6	390 368	18.4	16.3
Feb 10 / Aug 10	11	853 140	15.5	15.8
Aug 10 / Feb 11	15	1 137 021	15.8	15.8
Feb 11 / Feb 12	52	3 402 842	18.3	17.3
Feb 12 / Feb 13	33	4 415 694	9	13.8
Suicidal ideations				
Feb 09 / Aug 09	9	124 276	87	
Aug 09 / Feb 10	12	390 368	36.9	49 26.
Feb 10 / Aug 10	9	853 140	12.7	26.3
Aug 10 / Feb 11	22	1 137 021	23.2	25
Feb 11 / Feb 12	47	3 402 842	16.8	20.1
Feb 12 / Feb 13	50	4 415 694	13.6	17.4



PRAC comments:

In the previous PSUR-period, the incidence of suicidal events had not increased. However, the incidence of the most severe events (suicide attempt and completed suicide) had increased. The MAH was asked to follow up and comment upon this concern in the next PSUR (6). It was reassuring that the incidence of all categories of suicidal events decreased in this PSUR period.

In the clinical trials whole MDD population, all suicidal acts occurring during treatment or within the month following discontinuation of study treatment were taken into account.
All MDD patients, including bipolar I depressed patients, all treatment periods and study designs (open and controlled) were considered. In this larger population, the incidences of suicide attempts and completed suicides in the agomelatine 25/50mg group (0.6% and 0. 1%, respectively) were similar to those in the placebo group (0.8% and 0. 1%, respectively). Frequency of suicidal acts remained equivalent to figures (0.9%) found in the FDA database (Khan A, 2001). Incidence expressed in patient-months may compensate for the treatment duration difference, longer for agomelatine than for placebo and comparators. The analyses in patient-months confirm that agomelatine (0.3) did not increase the risk of suicidal acts compared to placebo (0.5) in the clinical studies.

The comparison between the 18-30 years age group and the > 30 years age group data regarding suicidal acts does not show a higher risk in agomelatine-treated younger adults. In particular, no completed suicide was reported in the 18-30 years age group in the short-term placebo controlled MDD set nor in the all MDD set.

The percentage of patients having attempted suicide was similar in the 18-30 years age group and in the > 30 years age group in the all MDD set either in the agomelatine group or the placebo group:

Table (16.4.2) 1 - Patients reporting a suicide attempt during study period in the updated All MDD Set (N=11823) - Analysis by treatment groups and age groups

All MDD set		Agomelatine 25-50 mg	placebo
Patients 18-30 years	N	1238	205
	n(%)	13(1.05%)	4 (1.95 %)
	pm	0.22	0.66
Patients > 30 years	N	6281	1188
	n(%)	35(0.56%)	7 (0.59%)
	pm	0.11	0.17

In post-marketing surveillance, suicidal events were reported for 333 patients, Suicidal Ideations being by far the most frequent event (151 cases), followed by Suicidal Attempts (116 cases) and Completed Suicides (52 cases).

No statistics can be conducted for this population. However, considering the known high natural frequency of suicidal events in depressed population and the number of patients already treated with agomelatine (10 279 401 patients-months), there is no evidence of either an increased frequency, greater severity, nor of clinical specificities of suicidal events reported for agomelatine-treated patients.

In the younger patients, post marketing data also do not evidence such a higher risk of suicidal events, with 13 reported cases of Suicidal Intention (out of 151), 20 reported cases of Suicidal Attempt (out of 116) and no 2 cases of Completed Suicide (out of 52) occurring in subjects up to 30-year old.

Conclusion

Taken altogether, neither clinical studies nor post marketing data evidenced a specific suicidal risk nor an at-risk population associated with the use of agomelatine. In most of the cases, patients presented with relevant medical history and/or relevant context and/or triggering factors. No increased risk was identified in young adults and elderly patients.
No new safety information regarding suicidal events emerged from this analysis. Suicide events remain under close monitoring.

PRAC comments:

The PRAC does not agree that the percentage of patients having attempted suicide was similar between the 18-30 years age group and in the > 30 years age group.
The percentage of persons having attempted suicide was higher in patients aged 18-30 years compared with patients > 30 years. However, this has been addressed in the following statement in the SmPC:

"A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders, showed an increased risk of suicidal behaviour with antidepressants compared to placebo, in patients less than 25 years old."

Concerning elderly patients, no data have been submitted, and the risk of suicidality could not be assessed in this group of patients. The MAH was requested to present data in the next PSUR on the frequency of suicidal events in elderly people (> 65 years) and compare with frequencies in younger age groups.

Important potential risk- Skin reactions

Skin reactions have been considered as important potential risk.

Based on the available information, the MAH proposes to no longer consider this risk as important.

The cumulative review of cases originating from post-marketing notifications showed:

A trend for decrease over time in frequency since Market Authorisation; the reported incidence of Skin reactions (serious and non-serious) reported within the last period covered (February 2012 – February 2013) (39.0 / 100 000 patient-years) was lower than the cumulative incidence since Market Authorisation (50.7 / 100 000 patient-years).

Most of the events (87%) are non-serious: over the 48-month period of post-marketing surveillance, 618 skin reactions were reported in 434 patients, including 536 non serious events. Most of the reported events (84%) were listed events.

Potential severe, drug-related cases were extremely rare, and in most of these cases, the diagnosis and / or the role of Agomelatine seemed questionable. From post-marketing surveillance, two life-threatening events were reported:

- One case of Stevens Johnson Syndrome which occurred after 6 months of treatment in a patient concomitantly treated with quetiapine. Diagnosis was confirmed by a dermatologist and the role of Agomelatine was assessed as unlikely (inadequate time to onset).
- One case of Toxic Epidermal Necrolysis which occurred after 9 days of treatment. The role of Agomelatine was assessed as doubtful.

No fatal case was reported since Market authorization.

In completed clinical trials, no serious cutaneous adverse events occurred since Market Authorisation.

PRAC comments:

A prospective observational study (CLE-20098-068) was ongoing and intended among other things, to study skin reactions. The PRAC considered that skin reactions should be an important potential risk until this study is finalized in 2015.

Important missing information – pregnancy and breastfeeding

Since Market Authorization, 87 cases of pregnancy were reported (including 49 pregnancy follow-ups), associated with 4 cases of breastfeeding. Patients were aged between 18 and 44 years; 21 had history of full-term pregnancies. Among these 87 cases, 77 patients were exposed to Agomelatine during the 1st trimester of pregnancy; 12 during the 1st and 2nd trimester, and 7 patients during the whole pregnancy. Four patients were only exposed to Agomelatine during the 2nd trimester, two in the 3rd trimester and one in the 1st and 3rd trimesters of pregnancy.

The pregnancy outcome was spontaneous abortion or foetal death in 9 cases, and spontaneous delivery without abnormalities in 35 cases.

Pregnancy outcome	Cumulative data since MA (N=87)
Spontaneous abortion	5
Induced abortion	10
Foetal death	4
Live birth	37
- Normal baby	35
- Congenital anomaly	2
Lost to follow-up	13
Follow-up in progress	18

The MAH has concluded that no new safety insight to agomelatine safety was provided from these cases.

PRAC comments:

According to the analysis presented by the MAH, alternative causes of the observed pregnancy outcomes were identified in many of these cases, thus no new conclusions with regards to agomelatine safety in pregnancy could be drawn from these reports. Four (4) cases of drug exposure during breast feeding were reported. No adverse events were reported from these 4 cases.

Important missing information – hepatic impairment

Since Market Authorization, 1 case was reported in a patient with a medical history of Hepatic impairment, from post-marketing sources. The patient had a medical history of hepatopathy and presented with CRP, ALT, AST and GGT increase 3 weeks after Agomelatine initiation. Agomelatine was stopped. The patient recovered from ALT and AST increase (recovering for GGT increase, unknown outcome for CRP increase).

The MAH concluded that this case did not provide any new safety insight to Agomelatine safety. This was endorsed by the PRAC.

Important missing information – severe and moderate renal impairment:

Since Market Authorization, 19 cases were reported in patients with a medical history of

Renal impairment, from post-marketing sources. Out of these 19 patients, 4 presented with Liver adverse reactions. No event was reported more than 3 times.
The MAH concluded that these cases did not provide any new safety insight to Agomelatine safety.

PRAC comments:

Cumulatively there were 19 reports of adverse events in patients with a history of renal impairment. There did not seem to be any pattern indicating a higher risk of a particular adverse event in patients with renal impairment. Overall, these data did not indicate any increased risk of adverse events in patient with renal impairment, however, no firm conclusions could be drawn.

Important missing information- Elderly

716 events have been reported cumulatively in 220 patients aged 75 years and over. The frequent unlisted events were confusional state (11 cases), drug ineffective (10 cases) and hyponatraemia (9 cases).

Important missing information- Paedriatic population

Cumulatively, 96 events were reported in 44 patients aged under 18 years. No risk factors can be derived from these data.

Discussion and conclusion on signal and risk evaluation

No new findings with regards to hepatotoxicity were identified from the data presented in this PSUR.

Concerning the important potential risk of suicide, the updated data was reassuring. Both the interval reported and cumulative incidences of suicidal events decreased as compared with previous PSUR periods. However, the risk of suicidal events in elderly patients could not be assessed as no data were submitted. The MAH was asked to comment on this issue in the next PSUR.

The PRAC considered that skin reactions should remain to be an important potential risk until the prospective observational study (CLE-20098-068) is finalized in 2015.

The MAH was asked to include restless leg syndrome, tinnitus and convulsions as ADRs in section 4.8 of the SPC and to update the he Package leaflet accordingly.

There was evidence that agomelatine could induce hyponatraemia. To elucidate this further, the MAH was asked to submit narratives for all cases that were not submitted previously, including narratives for the six latest reported cases.

No other risk minimisation activities were deemed necessary.

Effectiveness of risk minimisation

Additional risk minimisation measures were implemented for the important identified risk of hepatotoxicity. A DHPC as well as an updated educational material, were distributed towards the end of 2012 to inform about serious hepatic ADRs that were associated with agomelatine. Additionally, prescribers were advised to strictly adhere to the treatment recommendations in the SmPC.

The educational material also gave information on the contraindications for the concomitant use of agomelatine and potent CYP 1A2 inhibitors (i.e. ciprofloxacin and fluvoxamine).

The MAH was in the process of performing a prescription survey (MEA 005) to evaluate the effectiveness of this risk minimisation measure. The protocol was previously approved by CHMP, with a planned submission date in December 2013.

3. Benefit evaluation

Important baseline efficacy and effectiveness information

Agomelatine is indicated in the treatment of major depressive episodes in adults. At the time of grant of marketing authorisation in 2009 the CHMP considered that the magnitude of the short-term efficacy was not similar to the effect generally shown for the SSRIs. However, the effect demonstrated in the second relapse prevention study was in line with what has been shown for the SSRIs. The CHMP concluded that with the proposed liver monitoring program, and considering the otherwise favourable safety profile compared to other antidepressants, the effect magnitude demonstrated was sufficient to provide a clinically valuable alternative in the antidepressant treatment armamentarium for some patients.

According to the MAH, results observed with agomelatine in 6 new head-to-head short-term studies with different active comparators (Fluoxetine, Paroxetine, Sertraline, Escitalopram) support both the efficacy of agomelatine in MDD (HAM-D17 scale) and its magnitude of effect, being comparable to those of other first line reference antidepressants treatments.

The MAH claimed that in view of the distinct pharmacological profile of agomelatine, translating into additional clinical benefits (early alleviation of sleep disturbances and daytime drowsiness and improved tolerability profile compared to the SSRI/SNRIs group) this has been enriched with new data on sleep and daytime functioning vs. escitalopram (Quera-Salva et al., 2011; Corruble et al., EPA 2011) and on emotional processing in three studies.

Efficacy and safety of agomelatine was also investigated in patients with generalized anxiety disorder (GAD). Short term and long term efficacy (HAM-A scale) were demonstrated in two studies, according to the MAH.

Newly identified information on efficacy and effectiveness

Since the MA in 2009, the MAH completed 6 short-term studies (8-12 weeks duration): **CL3.045**, **CL3.046**, **CL3.048**, **CL3.052**, **CL3.056**, and **CL3.063** vs. active comparators. These studies had not been assessed by the CHMP at the time of this report. The main efficacy results of these new studies are briefly discussed below.

Study **CL3.045** was a direct, short-term (8 weeks) comparison of agomelatine versus fluoxetine. Change on the HAMD-17 scale was the main efficacy criterion. A total of 504 patients with severe depression (baseline HAM-D total score ≥ 25) were enrolled in Western Europe/Latin America and randomised to agomelatine 25-50 mg/day or fluoxetine 20-40 mg/day. Results for the primary efficacy endpoint are shown in Table 1; superiority over fluoxetine was claimed (p=0.024). Responder rates at Week 8 are shown in Table 2.

Study **CL3.052** had a similar design as study CL3.045, but was only conducted in Asian countries. A total of 609 patients with severe depression were randomised to agomelatine 25-50 mg or fluoxetine 20-40 mg/day. Results for the primary efficacy endpoint (HAMD-17 scale) after 8 weeks of treatment are shown in Table 1. Non-inferiority compared to fluoxetine was claimed based on a pre-defined non-inferiority margin of 1.5 (p=0.015); superiority was not shown. Responder rates at Week 8 are shown in Table 2.

In study **CL3.046** agomelatine 25-50 mg/day was compared with sertraline 50-100 mg/day. A total of 306 patients were randomised and followed up for 6 weeks. The primary aim of this study

was to study effects on different aspects of sleep and daytime condition; effects on depression were assessed with the HAMD-17 total score as a secondary endpoint (Table 1). Superiority over sertraline was claimed for this secondary endpoint ($p<0.001$). Responder rates at Week 6 are shown in Table 2. The short-term data from this study were already submitted during the MA procedure. It was concluded by the CHMP that although the magnitude of effect was considered to be of marginal clinical relevance (pre-specified efficacy analysis: difference HAMD-17 score = 1.68, $p=0.031$), it was concluded that agomelatine had documented some short-term efficacy.

Study **CL3.056** also aimed to study the effects of agomelatine on different aspects of sleep and daytime condition, and used HAMD-17 total score as a secondary efficacy criterion. In all, 129 patients were randomised to agomelatine 25-50 mg/day or escitalopram 10-20 mg/day. Non-inferiority, based on a pre-defined margin of 1.5, was claimed compared with escitalopram ($p=0.002$), Table 1). Superiority was not shown. Responder rates at Week 6 are listed in Table 2.

Study **CL3.063** had a similar design as study CL3.056 and aimed to study effects of agomelatine on various aspects of sleep and daytime condition. Changes on the HAMD-17 total score were assessed as a secondary efficacy criterion. Patients (n=321) were randomized to agomelatine 25-50 mg/day or escitalopram 10-20 mg/day. Results for the secondary efficacy endpoint are shown in Table 1. Non-inferiority versus escitalopram was claimed ($p=0.003$), based on a pre-defined margin of 1.5. Superioriy was not shown. Responder rates at Week 12 are listed in Table 2.

Study **CL3.048** aimed at studying the quality of sleep in patients aged >60 years old, and used HAM-D 17 total score as a secondary efficacy criterion. A total of 403 patients with severe depression were randomized to either agomelatine 25-50 mg/day, or paroxetine 20-30 mg/day. Results for the secondary efficacy endpoint are shown in Table 1. No statistically significant treatment differences for antidepressant activities were seen and superiority/non-inferiority versus paroxetine was not claimed. Responder rates at Week 12 are shown in Table 2.

Table 1. HAM-D total scores for new short-term efficacy studies (FAS; LOCF)

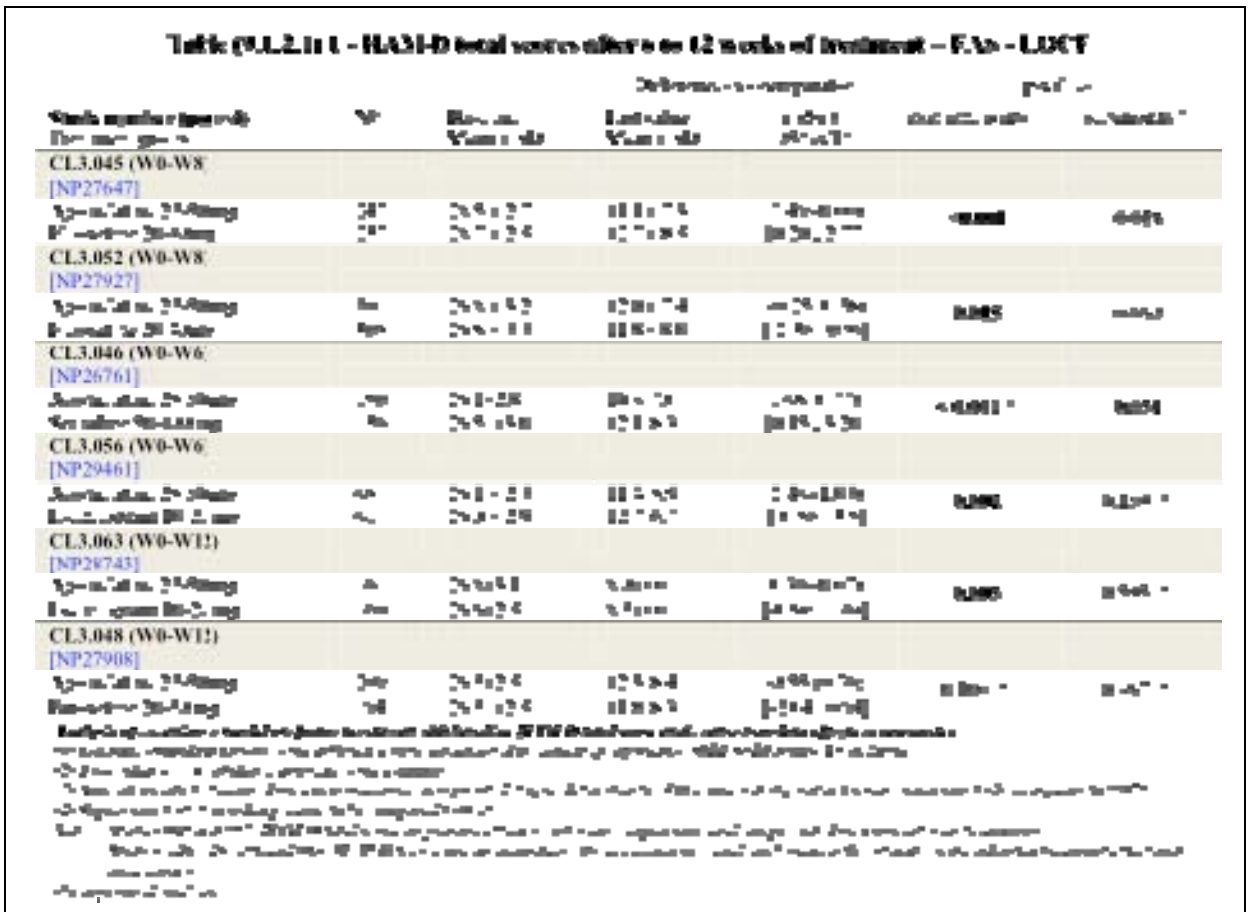
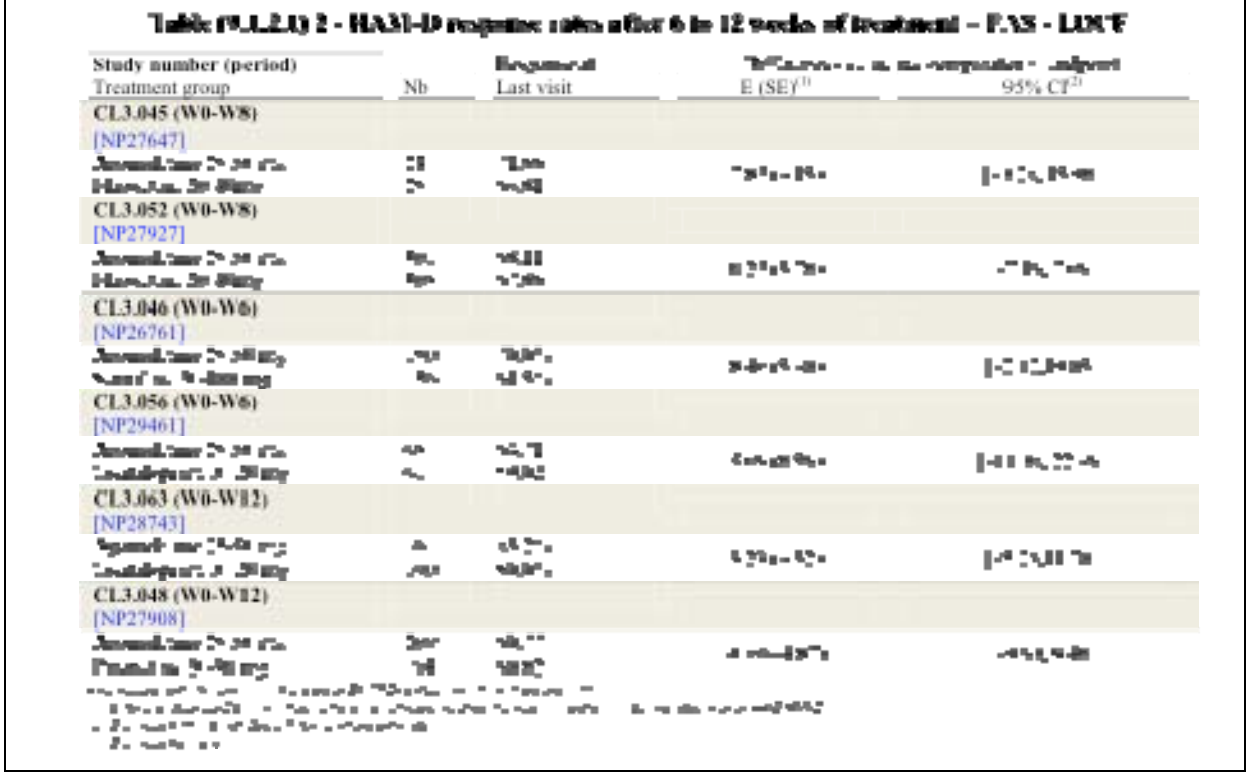


Table 2. HAM-D response rates for new short-term efficacy studies (FAS; LOCF)



Clinical studies in Major Depressive Disorder (MDD):

During the reporting interval, in two post commitment studies, agomelatine was according to the MAH found to be an effective treatment of Major Depressive Episodes, either in adult (CL3.069) or in elderly (CL3.070) populations. In both cases, magnitudes of the effects in terms of HAM-D total scores or responder rates favourably compared to those reported in recently published comparable studies with existing SSRIs/SNRIs according to the MAH's analysis. CL3.069 study evidenced a dose response for agomelatine, with both superiority of the 10 mg dose over placebo and superiority of agomelatine 25 mg and 25-50 mg over both agomelatine 10 mg and placebo (HAM-D17 scale). This study confirmed the effective dosage range, with the recommended therapeutic doses (25 mg and 25-50 mg) being the best therapeutic options. In CL3.070 study, observed differences on HAM-D17 scale between agomelatine (25-50 mg) and placebo were also statistically significant. In the sub-population of patients under 75, i.e. the recommended target elderly population for agomelatine treatment, the results favourably compared with the rare positive studies reported with other antidepressants in similar populations (Raskin et al., 2007; Schneider et al., 2003; Sheikh et al., 2004; Rapaport et al., 2009; Rapaport et al., 2003; Tedeschini et al., 2011; Katona et al., 2012) and demonstrated the antidepressant efficacy of agomelatine in elderly patients up to 75 years old.

PRAC comments:

Study CL3.069 was evaluated by the CHMP and the committee considered that the study did not have a design to allow conclusion regarding the efficacy of increasing the dose to 50 mg in patients not responding to 25 mg. For the two groups (25 mg fixed and 25-50 mg) the results were considered clinically relevant compared to placebo, however, the difference between the two groups was marginal. It was concluded that the data indicated that some patients may still benefit from an increased dose compared to those continuing on the 25 mg dose. However, the risk of liver related ADRs was increased on the higher dose. The MAH proposed the following for inclusion in section 4.2 of the SmPC:" **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.**" to reflect the increased risk with the higher dose. This amendment was endorsed by the CHMP. Accordingly, the MAH was requested to apply for a type II variation to include this information in the SmPC.

Study CL3.070 (FUM 002) was assessed by the CHMP. The aim was to study the efficacy and safety of agomelatine (25-50 mg/day) for 8 weeks in elderly patients suffering from MDD. A total of 218 patients were randomized to either agomelatine 25-50 mg/day or placebo. An optional double-blind extension period up to 16 weeks was scheduled for this study. Out of the 222 randomised patients, 175 (79 %) completed the mandatory W0-W8 period and 146 (66 %) entered the double-blind extension period. The clinical study in patients 65 years and older, revealed a statistically significant difference on the primary endpoint, HAM-D 17, between the agomelatine group and the placebo group in the full analysis set. The clinical relevance seemed modest; however, it was in line with the effect observed for agomelatine in other clinical studies in younger adults. On the contrary, no effect was documented for the sub-group of patients ≥75 years. In addition, the exposure of agomelatine was shown to increase several fold in this age group compared to patients <75 years. The MAH was requested to submit a Type II variation and the SmPC were amended in order to reflect the results achieved in elderly patients.

The MAH has since grant of MA completed 9 nine new randomised double-blind studies (2 placebo-controlled and 7 active controlled studies) including 3347 patients. In addition, 4 new studies (1 active controlled and 3 placebo-controlled studies) enrolling a total of 1660 patients with MDD have been conducted in the US by a Servier licensee,. Based on an assessment of the main results of these 13 new clinical studies, enrolling approximately 5000 patients with MDD, the overall efficacy

of agomelatine in the currently approved indication was considered modest, but generally in line with findings from previously submitted and assessed studies that formed the basis for the EU approval in 2009. However, in some studies treatment with agomelatine was not superior to placebo and/or an active control (SSRI/SRNI).

Characterisation of benefits

Overall, following the evaluation of studies submitted since grant of MA, the efficacy in the approved indication was considered modest, but in line with findings from the studies forming the basis for the EU approval in 2009.

During the reporting period an effect in patients above 65 years of age was shown in line with the effect seen in younger adults, however, no effect was seen in patients ≥75 years.

Discussion on benefits

Based on an assessment of the main results of 13 new clinical studies enrolling approximately 5000 patients with major depressive disorder, the overall efficacy of agomelatine based on short- and long-term outcomes on the HAM-D scale was considered modest, but generally in line with findings from previously submitted and assessed studies that formed the basis for the EU approval in 2009.

In some of the newly performed studies, treatment with agomelatine was not superior to placebo and/or an active control (SSRI/SRNI). Differences on the HAM-D scale were, however, rather small and the clinical relevance of these findings could be questioned.

4. Benefit-risk balance

The clinical efficacy on major depression was considered modest, however agomelatine has characteristics distinct from other antidepressants that may be valuable for a subset of patients, such as a positive effect on sleeping disturbances, a prominent symptom of major depression. Among the risks identified with agomelatine, hepatotoxicity was considered to be the most important. This caused concern, but it was decided that the risk might be acceptable provided that the recommendations in the SmPC were strictly followed. The overall benefit-risk balance of agomelatine in the treatment of patients with MDD remained positive.

5. Comments from Member States

General comments:

The severity of the cases of hepatotoxicity in the context of additional risk factors were worrying and further risk minimisation measures should be implemented (see below).

In term of efficacy, the new US placebo controlled efficacy studies should be assessed by the CHMP (the comparative studies with active arm without placebo arm were not considered methodologically adequate, to allow the assessment of the benefit of agomelatine as assay sensitivity was not ensured).

Hepatotoxicity

It was agreed that hepatotoxicity remained the main safety concern for agomelatine. Four months after the dissemination of the DHPC and updated educational material, the risk minimisation measures did not seem to have any major impact on reducing the number of serious hepatotoxic reactions or improving compliance with the SmPC, as supported by the PSUR data. The effectiveness of these measures should be further investigated through the prescription survey

performed by the MAH (study report submission in December 2013). However, there were doubts about the additional value of the prescription survey on this issue.

For that reason the following additional risk minimisation measures and updates of the SmPC were proposed:

→ The monitoring of liver function in section 4.4 of the SmPC should be included in bold type within a black box according to the Guideline on Summary of product characteristics (September 2009, rev. 2) in order to attract the prescriber's attention on this risk and the importance to perform monitoring of liver function.

→ An elevation of transaminases > 3 times the upper limit of the normal range should be reinforced as a contraindication.

→ An abdominal ultrasound should be recommended at initiation of Valdoxan.

→ It should be stated in section 4.8 that few cases of hepatic failure were reported with fatal outcome or liver transplantation in patients with hepatic risk factors.

→ The treatment should be initiated and supervised by a physician experienced in depression as an additional risk minimisation measure.

Rationale:

During the covered period, 2 fatal cases of hepatic failure were reported in the context of alcohol consumption. The role of agomelatine as having an additive deleterious hepatic effect in patients with substantial alcohol intake is likely. No information on monitoring of liver function at Valdoxan initiation was provided for these 2 cases.

After the data lock-point, an additional case of acute hepatic failure was reported. The patient consumed alcohol for several years and experienced acute hepatic failure 30 days after Valdoxan initiation (bilirubin: 165mg/L, ALP: 152UI/L, GGT: 200UI/L, AST: 1739UI/L, ALT: 665UI/L, Factor V: 47%) that required Valdoxan discontinuation. No information on monitoring of liver function is provided. The patient had not recovered at the time of reporting.

Caution was recommended when prescribing Valdoxan for patients with hepatic injury risk factors as non-alcoholic fatty liver disease (section 4.4). As the monitoring of liver function detailed in the SmPC does not allow diagnosis of steatosis, an abdominal ultrasound should be recommended at initiation of Valdoxan.

Considering preliminary data from the prospective observational study (CLE-20098-068), the recommendations in the SmPC did not seem to be systematically strictly adhered to (i.e initiation of Valdoxan in patients with an increase in transaminases exceeding 3X upper limit of normal at baseline). Therefore, an elevation of transaminases > 3 times the upper limit of the normal range should be reinforced as a contraindication.

The treatment should be initiated and supervised by a physician experienced in depression in order to ensure an optimal benefit / risk assessment on an individual basis.

Elderly patients

The clinical study CL3.070 concluded to a modest clinical relevance of agomelatine in patients 65 years and older; however it was in line with the effect observed for agomelatine in other clinical studies in younger adults. On the contrary, no effect was documented for the small sub-group of patients ≥ 75 years. The CHMP concluded that agomelatine should not be used by patients in this age group which is stated in section 4.4 of the SmPC. In order to attract the prescribers' attention on this recommendation for this vulnerable population, it should also appear in the section 4.2 of the SmPC.

An analysis of suicidal events in elderly patients (> 65 years) and a cumulative review of post-marketing cases reported in patients 65 years and older (≥ 75 years) since Valdoxan market was recommended to be performed.

Regarding that no effect was documented for the sub-group of patients ≥ 75 years and the higher vulnerability of this population, Valdoxan use in elderly patients should continue to be closely monitored and a new study in this population should be performed. Without this commitment, a contradiction in patients ≥ 75 years should be discussed.

Hyponatremia

Evidence was presented indicating a causal relationship between agomelatine and event of hyponatremia. Hyponatremia should be listed in the section 4.8 as post-marketing event provided that this signal is confirmed further to analysis of narrative cases. A warning concerning this adverse reaction should also be added in section 4.4 of the SmPC.

PRAC position:

Introduction of black box:

In accordance with the SmPC Guideline, especially important safety information may be included in bold type within a box in exceptional cases. This is a measure rarely used in EU SmPCs. The warning regarding hepatotoxicity already has a central placement at the top of section 4.4 in the Valdoxan SmPC. Additionally, the risk of hepatotoxicity has also been clearly communicated through Dear Healthcare Professional Communication and Educational Materials. The additional benefit of introducing a "black box" is therefore considered to be marginal, and it could be questioned if the requirements for "exceptional cases" are fulfilled, in accordance with the SmPC guideline. Overall, the PRAC did not support the proposal to introduce a black box.

Introduction of elevated transaminases > 3 ULN as a contraindication:

In the SmPC it is stated that therapy should be discontinued if serum transaminases exceeds 3 X upper limit of normal. Regarding initiation of treatment, it is recommended to exercise caution when administering agomelatine to patients with pretreatment elevated transaminases (> the upper limit of normal ranges and ≤ 3 times upper limit of the normal range). Although these recommendations should be interpreted to not initiate treatment in patients with transaminases > 3 ULN, this is not explicitly stated in the SmPC. The addition of the proposed contraindication would therefore serve as a clarification of the current recommendations, and the proposal is therefore supported by the PRAC.

Recommendation to perform abdominal ultrasound:

The PRAC did not consider that it was warranted to introduce a recommendation to perform abdominal ultrasound in all patients prior to initiation of treatment. The SmPC includes a warning to exercise caution when prescribing agomelatine for patients with hepatic risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, substantial alcohol intake or concomitant medicinal products associated with risk of hepatic injury. The decision to perform any further

investigations such as abdominal ultrasound to elucidate potential hepatic risk factors should be left to the decision of the treating physician based on an overall evaluation of each individual patient. It was not considered appropriate to introduce a general recommendation for abdominal ultrasound in all patients, and it was considered that such a measure would be difficult to carry out in practice.

Update of section 4.8

The proposal to update section 4.8 of the SmPC with information of cases of fatal outcome or liver transplantation in patients with hepatic risk factors was supported. It was also considered that the same text should also be included in section 4.4.

Initiation of treatment by physician experienced in the treatment of depression:

Psychiatrists are best qualified in treating depression, however they are not in general expected to have any particular expertise in the monitoring and treatment of hepatotoxic reactions. Depression is also a frequent diagnose among patients treated by general practitioners, who are considered as well qualified for monitoring hepatic function as psychiatrists. The PRAC did not consider that the above proposal would be an efficient risk minimisation measure, and therefore did not support it.

The PRAC supported the proposal that information should be included in section 4.2 of the SmPC on the fact that agomelatine should not be used in patients ≥ 75 years of age. It was agreed that the use of agomelatine in this population, should be closely monitored in the following PSUR-period.

Study CL3.070 only included 48 patients receiving agomelatine. As antidepressant agents in general are frequently used in elderly patientsthe PRAC recommended reiterating the message to the prescribers with regards to the lack of efficacy in patients ≥ 75 years of age and risk of hepatotoxicity.

Concerning suicidality in elderly:

Suicidality is addressed in the SmPC. Section 4.4. contains the standard text on suicidality that is included in SmPCs of all antidepressants on the market. "Suicidal thoughts or behavior" is stated as an ADR in section 4.8. The MAH was requested to present in the following PSUR, data on frequency of suicidal events in elderly patients (≥ 65 years) compared with frequency in younger age groups. The PRAC did not consider that a cumulative review of post-marketing suicidal events in elderly patients would provide additional information. However, if the frequency of suicidal events in elderly patients, based on data from pooled clinical trials, turned out to be higher than in lower age groups, further activities may be warranted.

The proposal regarding hyponatraemia was endorsed.

6. MAH's responses and comments to the preliminary assessment report:

6.1. Request for supplementary information

There is some evidence that agomelatine can induce hyponatraemia. However, to elucidate this in more detail, the MAH is asked to submit narratives of all cases previously not submitted.

The MAH has submitted case narratives for all cases of hyponatraemia previously not submitted (20 cases).

In total 33 cases of hyponatraemia were reported to the MAH.

PRAC comments:

The additional cases did not provide further evidence on the association of agomelatine with hyponatraemia. Alternative explanations were present in most cases, like concomitant drugs and/or vulnerability of the patient to hyponatraemia. In other cases sufficient information was lacking to assess causality (i.e. information on time relationship and/or outcome).

Hyponatraemia is labeled for most of the other classes of antidepressant drugs like tricyclics, SSRI, SNRI and mirtazapine. However, agomelatine has a different mechanism of action than these drug classes (melatonin-agonist (MT1-and MT2) as well as a 5-HT2c-antagonist).

The PRAC considered that evidence was not sufficient to establish a causal relationship between agomelatine and hyponatraemia.

In future PSURs, the MAH was requested to present narratives of all new cases of hyponatraemia. Special attention should be paid to cases with positive rechallenge, positive dechallenge and cases recovering during continuous treatment. Efforts should be taken to collect all relevant information to assess causality for these cases.

Based on the review of data on safety and efficacy, the PRAC considered that the risk-benefit balance of medicinal products containing the active substance agomelatine remained favorable, but recommended that the terms of the marketing authorisation(s) be varied as described:

- **Update of section 4.8 of the SmPC to add restless leg syndrome with a frequency ≥ 1/1000 – 1/100**
- **Update of section 4.8 of the SmPC to add tinnitus with a frequency ≥ 1/100 to <1/1**
- **Update of section 4.8 of the SmPC to add convulsions with a frequency ≥1/10 000 to <1/1000**

The Package leaflet is updated accordingly.

MAH'S RESPONSE:

6.1.1. Restless leg syndrome

The MAH agreed to update section 4.8 with restless leg syndrome (frequency ≥ 1/1000 to < 1/100).

6.1.2. Tinnitus

The MAH consented to update section 4.8 with tinnitus. However, they argued that the frequency should be ≥ 1/1000 to < 1/100, and this was endorsed by the PRAC.

Table (2.2) 1 - Results on the incidence calculation for adverse drug reactions to be listed in the SmPC

Adverse drug reactions to be listed in the SmPC	Incidence in clinical trials		Corresponding MedDRA frequency
	Overall Safety Set Agomelatine 25/50mg (N=8410) n (%)	Placebo (N=1851) n (%)	
Tinnitus	38 (0.45%)	3 (0.16%)	Uncommon [≥1/1000 to <1/100]

6.2. Convulsions

Further to PSUR 6 PRAC preliminary assessment report on 8th July 2013, MAH was requested to include Convulsion in section 4.8 of Valdoxan SmPC as rare adverse reaction.

In view of the update of data from post-marketing as well as further explanation regarding preclinical and clinical data, the MAH still considered convulsion as a false signal and proposed not to incorporate this event in section 4.8 of Valdoxan SmPC

Preclinical data used to support the MAH position

Several preclinical studies have shown the anticonvulsant properties of melatonin in different rodent models (mice, rat, guinea pigs) of epilepsy. In the amygdala kindled rats (established model for temporal lobe human epilepsy), melatonin (75mg/kg, i.p. acutely) increased the after-discharge threshold and suppressed generalized seizures (Mevissen et al., 1998). In models of epilepsy induced by drugs (pilocarpine, penicillin, pentetrazole, kainate) or electroshock, melatonin (10-80mg/kg i.p. or 40-80µg i.c.v. acute or chronic treatment) increased the latency and decreased the frequency of convulsions in rats (Costa-Lotufo et al.,2002; Yildirim and Marangoz, 2006; Tchekalarova et al., 2013) and guinea pigs (Solmaz et al., 2009), and increased the seizure threshold in mice (Borowicz et al., 1999; Yahyavi-Firouz-Abadi et al., 2006). Moreover the selective melatonin receptor ramelteon (200mg/kg 5 days) attenuated seizure periodicity and frequency in the mice lacking the potassium channel subunit KCNA1 chronic epilepsy model (Feneglio-Simeone et al, 2009). In clinics, several data from clinical studies and case reports are in line with a beneficial effect of melatonin in epileptic patients. Indeed, chronic melatonin (3-50mg) reduced the seizure frequency, an effect mainly in children and adolescents (Molina-Carballo et al., 1997; Fauteck et al., 1999; Peled et al., 2001; Jones et al., 2005; Uberos et al., 2011, Goldberg-Stern et al.,2012). Preclinical safety pharmacology studies have shown that agomelatine had a protective effect against electroshock-induced convulsions in mice (32 and 128 mg/kg NP08127). In rats agomelatine (64 and 128 mg/kg) increased the ECS threshold (NP15704). In line with these data the anticonvulsivant effects of agomelatine (25-75 mg/kg i.p. acutely) on pentylenetetrazole and pilocarpine-induced convulsions by increasing convulsions latency has been described (Aguiar et al, 2012).

Globally, the data from preclinical studies were in favor of the anticonvulsant effects of melatonin agonists and specially agomelatine. Furthermore, melatonin was shown to have anticonvulsant effects in epileptic patients.

PRAC comments:

Safety pharmacology studies with agomelatine and melatonin have demonstrated increased electroconvulsive threshold in mice and rats, indicating lack of a pro-convulsive effect of agomelatine. Further, no seizures were reported in general toxicity studies with agomelatine in

rats and monkeys. In line with these findings, the MAH provided literature references, all indicating anti-convulsive effects of melatonin-receptor activation in different animal models.

In conclusion, existing non-clinical data did not indicate a pro-convulsive effect of agomelatine.

Although preclinical data are not necessarily relevant for humans, these data provided an element of uncertainty to the recommendation that section 4.8 of the SmPC should be updated with "convulsions".

As regards melatonin an article in the journal «Drug Safety» concluded that there was clearly a need for large randomized, double-blind, placebo-controlled trials to establish the role of melatonin in either predisposing to or decreasing the likelihood of seizures. However, the limited human data and considerable animal work suggest that melatonin was unlikely to cause significant seizure exacerbations and, perhaps in higher doses, might have antiepileptic properties.

(Siddharth Jain, Besag FMC. Does Melatonin Affect Epileptic Seizures? Drug Saf 2013; 36:207-215).

Phase II and III Clinical data to support the MAH position

The Integrated Analysis of Safety was performed on data from forty six (46) completed clinical studies. The 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…). It consists in 9364 patients who received agomelatine (8410 patients received agomelatine 25/50 mg), 1851 received placebo and 2604 received an active control (fluoxetine, paroxetine, venlafaxine, escitalopram, sertraline or duloxetine).

Five cases of Seizures on agomelatine (dose 25/50 mg) out of 8410 agomelatine-treated patients (0.06%) were reported as an adverse event during phase II and III development program.

Among those 5 cases, the following PT terms were recorded: 2 cases of Convulsion, 2 cases of Epilepsy and 1 case of Grand mal convulsion.

Among 5 patients, 2 had a medical history of epilepsy. The event was serious in both cases. One other patient had a medical history of syncope, a familial history of epilepsy and the urine THC (TetraHydroCannibinol) test was positive while seizures occurred (concomitant use of cannabinoids). In two remaining patients, the event occurred 366 days after the first intake of the study drug in the first case and 365 days after the study beginning (and one day after the last study drug intake) in the second one. In this last patient, the seizures occurred in the context of venipuncture (3 attempts).

In conclusion, no particular concern rose from the analysis of these 5 cases.

PRAC conclusion:

It was agreed that causality seemed doubtful for the two cases occurring one year after treatment initiation. For the other cases information was too scarce to assess causality.

To assess causality in more detail, narratives for the cases seen in clinical studies were asked to be provided in the following PSUR.

Post-marketing data

Pr. 22 July 2013, 44 cases have been reported.

Table (2.3.3) 1 - Convulsion: post-marketing data assessment (based on the data available on 22 July 2013)

CLINICAL RELEVANCE	
Number of cases since MA	44 (38 HCP cases) (4.3/100 000 PY)
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 17/44 Within 1 month: 8/44 > 1 month: 12/44 Unknown: 7/44
Causality assessment	Doubtful: 43/44 Likely: 1/44 (further detailed below)
Dechallenge/Rechallenge	Positive dechallenge: 22/44 Positive rechallenge: 1/44
Alternative explanation	Overall, 32 patients amongst the 44 (73%) had a relevant context, medical history or concomitant medication that could explain convulsions.

	Relevant medical history: 17/44 • Epilepsy / Convulsion: 14/44 • Glioma: 1/44 • Temporal lobe sequelae due to surgery: 1/44 • Cerebrovascular accident/disorder: 3/44 • Craniectomy: 1/44 • Alcoholism: 1/44 Relevant context: 16/44 • Benzodiazepine/SSRI/SNRI abrupt discontinuation or tapering: 6/44 • Discontinuation of antiepileptic treatment: 2/44 • Overdose : 2/44 (1 with bupropion 1 with sertraline both known to induce convulsion) • Patient treated for drug addiction: 1/44 • Serotonin syndrome : 2/44 • Worsening of epilepsy: 1/44 • Diabetic hyperosmolar coma: 1/44 • Sleep deprivation: 1/44 • Alcohol heavy consumption: 1/44 Concomitant drugs: 17/44 including Bupropion, Lithium, SSRI, SNRI, Triptans.

Serious (Fatal) cases	42/44 including 3 fatal cases: • in one case, a patient with a medical history of glioma experienced an epileptic crisis while she was driving. She eventually died as a result of the car accident. • in one case the patient died from an umpteenth epileptic crisis due to the evolution of her medical history (fatal familial insomnia). • in the remaining case, the outcome of epilepsy was not recovered but the case was fatal as, the patient died on the following day from diabetic hyperosmolar coma.

Outcome of the event	Recovered: 29/44 (including 5 patients recovered under treatment) Recovered with sequelae: 1/44 Not recovered: 2 /44 Fatal: 2/44 Unknown: 10/44
Disproportionality analysis	Similar with AGOMELATINE in comparison to all other Servier drugs (0.30% vs 0.18%, respectively)

In 50% of the cases, dechallenge was positive, however, this concept is difficult to take into account when events occur as crisis that by nature is an event with a brief duration. Evolution was favourable in 85% of the cases with documented outcome. Five patients recovered under treatment. Amongst these 5 cases, follow up information was provided for 3 cases and no convulsive crisis reoccurred from 1 to 3 months after the initial event, although patient remained under Valdoxan. Eight patients amongst the 44 presented with neurological exploration such as Brain CT scan, MRI and/or EEG.

No new safety concern arose from the post-marketing analysis of the cases of Convulsion and related terms.

PRAC comments:

It was agreed that cases with positive dechallenge were difficult to interpret.

The case with positive rechallenge was previously discussed in this report.

It should be noted that 5 patient had a favorable outcome while agomelatine was maintained at the same dosage. Narratives for these cases were asked to be provided in the PSUR to follow.

Narratives should also be submitted for the 8 patients with neurological exploration.

Overall the MAH considers that the data from preclinical studies were in favour of the anticonvulsant effects of melatonin agonists and specially agomelatine. Five cases of Seizures on agomelatine (dose 25/50 mg) out of 8410 agomelatine-treated patients (0.06%) were reported as an adverse event during phase II and III clinical trials.

44 cases have been reported post-marketing. The review of data from post marketing surveillance showed that 73 % of the patients had a relevant context, medical history or concomitant medication that could explain convulsions.

All cases presented with imputability assessed as doubtful except 1 case, assessed as likely because of positive rechallenge, in a patient with untreated well known medical history of epilepsy, which was poorly documented. The MAH considered that this case did not raise any safety concerns. In 50% of the cases dechallenge was positive, however, this concept is difficult to take into account when events occur as crisis that by nature is an event with a brief duration.

In accordance, the signal "Convulsion" remains a false signal and the MAH argued that it was not relevant to update the SmPC and leaflet accordingly.

PRAC comments:

Preclinical data did not indicate a pro-convulsive effect of agomelatine. Safety pharmacology studies with agomelatine and melatonin demonstrated increased electroconvulsive threshold in mice and rats.

An article published in the journal "Drug Safety" concluded that there was limited human data and considerable animal work suggesting that melatonin was unlikely to cause significant seizure exacerbations and, perhaps in higher doses, might have antiepileptic properties. However, large randomized double blind and placebo-controlled trials were recommended as needed to assess the role of melatonin as regards effect on convulsions.

As previously discussed, human data on the possible association between agomelatine and convulsions remained difficult to interpret.

Based on the totality of preclinical and clinical data, the PRAC endorsed the opinion that it was too premature to include "convulsion" as an ADR in section 4.8 of the SPC. The MAH was requested to submit narratives of all cases of convulsions reported in the PSUR (7) period to follow, where the causality between agomelatine and convulsions could be re-evaluated.

6.3. Study CL3-20098-073:

The MAH should consider whether treatment recommendations when therapy is switched from another antidepressant therapy (SSRI or SNRI), can be derived from this study. If so, treatment recommendations should be included in the SmPC as this is clinical important information for the prescriber.

RESPONSE

In view of the above mentioned assessment's comment the MAH proposes to submit a variation within 2 months after the end of the renewal procedure and PSUR assessment procedure in order to reflect in the SmPC treatment recommendations when therapy is switched from another antidepressant therapy (SSRI or SNRI) derived from the CL3-20098-073.

PRAC comments:

The above proposal was supported.

7. Literature

The PRAC-Rapporteur has recently been made aware of a publication describing two cases of delirium associated with agomelatine*. Positive rechallenge was noted in both cases.

At DLP of PSUR 6, there were 9 cases of delirium and 2 cases of delirium tremens in the MAH's database. There were 56 cases of "confusional state". In addition, the following ADRs are stated in section 4.8 of the SPC: agitation, irritation, aggression and hallucinations.

The authors discuss that delirium may possibly involve the melatonin-receptors MT1 and MT2, as hallucinations, amnesia, agitation and behavioral changes have been reported for the selective MT1/MT2-agonist ramelteon.

In the next PSUR the MAH was asked to perform a cumulative review of cases of delirium and discuss whether delirium should be stated as an ADR in section 4.8 of the SPC.

*Sacha MGV, Ambrosi B, Muñoz C et al. Two cases of delirium with agomelatine therapy. Annals of Clinical Psychiatry. 25(1):67-8, 2013 Feb.

8. Final assessment conclusions and actions

Data from PSUR no 6 did not change the benefit-risk profile of the product.

Based on an assessment of the main results of 13 new clinical studies, enrolling approximately 5000 patients with major depressive disorder, the overall efficacy of agomelatine based on outcomes on the HAM-D scale was considered modest, but generally in line with findings from previously assessed studies that formed the basis for the EU approval in 2009.

Hepatotoxicity remained the main safety concern. Data from this PSUR confirmed previous knowledge in this area. To clarify the recommendations in the SmPC, the PRAC considered that section 4.3 of the SmPC should be updated to include a contraindication in patients with transaminases exceeding 3 X upper limit of normal. Further to this, section 4.4 and 4.8 of the SmPC should be updated to include information on cases of hepatic failure reported with fatal outcome or liver transplantation in patients with hepatic risk factors. Otherwise, the risk minimisation measures were considered to be sufficient. The MAH was in the process of performing a survey to evaluate the effectiveness of these risk minimisation measures, the results of which were to be discussed in the following PSUR.

Skin reactions and suicide were still considered to be important potential risks of the product.

Restless leg syndrome, Tinnitus:

Restless leg syndrome and tinnitus were to be included as adverse reactions in section 4.8 of the SmPC with a frequency "uncommon". The package leaflet was to be updated accordingly.

Convulsions

Forty-four (44) cases were reported in the post-marketing period. About one-third of the cases occurred within a week after start of treatment, suggesting a time-relationship. Positive rechallenge was seen in one case, and positive dechallenge in 22 cases. The value of dechallenge in this context was, however, difficult to interpret as the event was of short duration. Clinical trial data showed no significant difference in the incidence of convulsions between agomelatine and placebo. However, data indicated a trend that the incidence was higher in the agomelatine-group (0,06%) vs placebo-group (0%).

Preclinical data demonstrated an increased electroconvulsive threshold of agomelatine and melatonin in mice and rats. A leading article in the journal "Drug Safety" concluded that based on preclinical and limited human data, melatonin was unlikely to cause significant seizure exacerbations and might even have antiepileptic activity in higher doses.

Based on the totality of data, the PRAC was of the opinion that it was too premature to include "convulsions" in section 4.8 of the SmPC. The causality between agomelatine and convulsions was to be re-evaluated following the next PSUR-period.

Hyponatraemia

Thirty-three (33) cases of hyponatraemia were reported. Positive rechallenge was seen in three cases, while positive dechallenge was seen in nine cases. Clinical trial data showed no significant difference in the incidence of hyponatraemia between agomelatine (0,06%) and placebo (0%), however, a trend indicating a higher incidence in the agomelatine-group could be seen.

There was evidence indicating that agomelatine could induce hyponatraemia. However, data were too scarce to establish a causal relationship. The causality was to be re-evaluated following the next PSUR-period.

Events under close monitoring

Pancreatitis, thrombocytopenic purpura, drug interactions with anticoagulants as well as use of agomelatine in patients ≥ 75 years, were recommended to remain under close monitoring in the following PSUR period.

The following events were decided not to be under close monitoring any longer: confusion, blood bilirubin increased, myalgia, blood pressure increased, alopecia, palpitations, oedema peripheral, panic attacks, muscle spasm, tremor and photosensitivity.

PSUR for the next period

The PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

The PRAC noted the MAH's commitment to submit a variation within 2 months after the end of the renewal procedure and PSUR assessment procedure in order to reflect in the SmPC treatment recommendations when therapy is switched from another antidepressant therapy (SSRI or SNRI) derived from the CL3-20098-073 study.

9. Request for supplementary information

In the next PSUR the MAH was asked to submit narratives for all the cases of hyponatraemia reported. Additionally they should submit narratives for:

- the 5 cases of convulsions reported with favourable outcome while agomelatine was maintained at the same dosage.
- the 8 cases with neurological exploration.
- cases of convulsions seen in clinical studies
- cases of convulsions reported in the next PSUR-period

10. Recommendations

Based on the review of data on safety and efficacy, the PRAC considered that the risk-benefit balance of medicinal products containing the active substance agomelatine remained favourable but recommended that the terms of the marketing authorisation(s) be varied as follows:

- Update of section 4.2 to state that agomelatine should not be used in patients ≥ 75 years.
- Update of section 4.3 of the SmPC to add transaminases exceeding 3X upper limit of normal as a contraindication.
- Update section 4.4 and 4.8 of the SmPC with information about cases of hepatic failure reported with fatal outcome or liver transplantation in patients with hepatic risk factors.
- Update of section 4.8 of the SmPC to add restless leg syndrome with a frequency ≥ 1/1000 – 1/100.
- Update of section 4.8 of the SmPC to add tinnitus with a frequency ≥ 1/1000 to <1/100
- The Package leaflet is to be updated accordingly.

Moreover, the PRAC recommended that a DHPC should be submitted to remind the prescribers on efforts to be taken to avoid serious hepatic ADRs. In addition, prescribers should be reminded that efficacy has not been shown in patients > 75 years and that agomelatine should not be used in this population.

The PRAC recommended that the PL should be amended with appropriate headings to attract the patient's attention to the information about potential serious hepatic ADRs and how to avoid them. This message needs to remain consistent with the relative sections of the SmPC.

In addition, the MAH was requested to address the following issues in the next PSUR:

- When analysing the effect of risk minimisation and compliance in future PSURs, the MAH should include analysis of whether liver function tests have been performed according to the SmPC.
- The MAH should present data on the frequency of suicidal events in elderly people (> 65 years) and compare with frequencies in younger age groups.
- The MAH should perform a cumulative review of cases of delirium and discuss whether delirium should be stated as an ADR in section 4.8 of the SPC.
- The MAH should perform a cumulative review of new cases of convulsions and hyponatraemia.

The following events should be under close monitoring in the next PSUR period:

- pancreatitis, thrombocytopenic purpura, drug interactions with anticoagulants and adverse events as well as lack of efficacy in elderly patients ≥ 75 years.