

## 1.1. An overview of reports on agomelatine

### Introduction

Agomelatine (Valdoxan<sup>®</sup>) was registered for the European market on February 19th 2009 and is indicated for *treatment of major depressive episodes in adults* [1].

The introduction of agomelatine added a new therapy to the arsenal of antidepressants. For its indication, tricyclic antidepressants are the first choice treatment, and the exact place of agomelatine in the treatment of this indication is yet to be determined [2]. Since Valdoxan<sup>®</sup> has obtained a market authorization from EMA, there has been some discussion regarding the risk-benefit balance of this drug. According to a recently published article, several international experts are not convinced agomelatine has additional value in the treatment of patients with major depressions [3] This prompted us to review and analyse the reports received by Lareb's spontaneous reporting system.

Agomelatine is a melatonergic (MT) agonist with high affinity for the MT1 and MT2 receptors. In addition, it is an antagonist for the 5-HT<sub>2c</sub> receptor. Binding studies indicate that agomelatine has no effect on monoamine uptake and no affinity for  $\alpha$ -,  $\beta$ -adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors.

In humans, agomelatine has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset [1].

On March 22, 2011 agomelatine (ATC code N06AX22) was not yet present in the GIP database. Therefore no data are available regarding the number of patients using agomelatine in the Netherlands [4].

In this overview the reports on this new drug received by Lareb through the spontaneous reporting system will be discussed.

### Reports of ADRs

On March 23, 2011 the Netherlands Pharmacovigilance Centre Lareb had received 39 reports related to the use of agomelatine. These reports contained a total of 93 possible adverse drug reactions.

Of these 93 reports, 30 were reported as serious according to the CIOMS criteria and of these, 15 were of neurological or psychiatric origin.

Table 1. Reported adverse events on agomelatine, grouped by system organ class received through spontaneous reporting (only the System Organ Classes containing ADRs are displayed).

System Organ Class	ADRs Lareb	ADRs in Lareb database	common and very common adverse drug reactions according to SPC
Blood and lymphatic system disorders	2	thrombocytopenia	-
Cardiac disorders	1	palpitations	-
Ear and labyrinth disorders	3	tinnitus	-

<b>System Organ Class</b>	<b>ADRs Lareb</b>	<b>ADRs in Lareb database</b>	<b>common and very common adverse drug reactions according to SPC</b>
Eye disorders	2	visual acuity reduced, vision blurred	uncommon: blurred vision
Gastrointestinal disorders	14	abdominal pain (n=3), abdominal pain upper (n=2), nausea, vomiting, eructation, constipation, gastritis, dyspepsia, faeces discoloured, GERD, abdominal distension	nausea, diarrhoea, constipation, upper abdominal pain
General disorders and administration site conditions	1	Death*	fatigue
Hepatobiliary disorders	1	abnormal hepatic function	increases in ALAT and/or ASAT
Injury, poisoning and procedural complications	1	intentional overdose	-
Investigations	7	weight increased (n=2), alkaline phosphatase increased, liver function test abnormal, hepatic enzyme abnormal, ALAT increased, GGT increased	increases in ALAT and/or ASAT
Metabolism and nutrition disorders	2	increased appetite, diabetes mellitus	-
Musculoskeletal and connective tissue disorders	4	back pain	back pain
Nervous system disorders	18	headache (n=6), somnolence (n=3), dizziness (n=2), crying, loss of consciousness, depressed level of consciousness, paraesthesia, hyperesthesia, involuntary muscle contractions, memory impairment	headache, dizziness, somnolence, insomnia, migraine
Psychiatric disorders	26	nightmares (n=4), insomnia (n=3),	anxiety, insomnia (in

System Organ Class	ADRs Lareb	ADRs in Lareb database	common and very common adverse drug reactions according to SPC
		aggression (n=3), anxiety (n=3), depressed mood, suicide attempt, completed suicide, suicidal ideation, agitation, dissociation, inappropriate affect, feeling guilty, somnambulism, tension, impulsive behaviour, fear, delusion	SOC nervous system) frequency not known: suicidal thoughts or behaviour
Renal and urinary disorders	1	urinary incontinence	-
Skin and subcutaneous tissue disorders	7	rash (n=2), eczema, acne, petechiae, dermatitis bullous, photosensitivity reaction	uncommon: eczema rare: erythematous rash
Social circumstances	1	physical assault	-
Vascular disorders	2	pallor, peripheral coldness	-

\* This report concerns a female aged 43 years with a history of suicide attempts and alcohol / drug abuse, who committed suicide 11 months after starting agomelatine for depression and lacosamide for epilepsy. According to the reporter the suicide was due to a lack of effect of the agomelatine treatment

The adverse drug reactions most frequently reported via the spontaneous reporting system are in general consistent with the ADR profile of agomelatine as reported in the SmPC. In most of the cases, if an ADR reported via the spontaneous reporting system is not present in the SPC, it was only reported once. One major exception to this observation is the occurrence of nightmares, which has been reported to Lareb four times and is not present in the SPC. This association will be described below in detail. Other reactions reported to Lareb that are not present in the SmPC, such as thrombocytopenia and tinnitus, will be monitored, and possibly analysed in the future.

### Nightmares associated with agomelatine use

The details of reports concerning nightmares in patients using agomelatine are presented in table 2.

Table 2. Reports concerning nightmares associated with the use of agomelatine

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 105851 F, 51-60 years	agomelatine 25mg sleep disorder	risedronic acid weekly tablet 35mg	headache, paraesthesia distal, abdominal cramps, nightmares, hard to awaken, sleep walking, nausea, fear	8 days unknown unknown
B 108202 M, 71 years and older	agomelatine 25mg depression		nightmares	2 days discontinued recovered
C 109434 F, 41-50 years	agomelatine 25mg depression		dizziness, nightmare	5 days no change unknown
D 109610 F, 31-40 years	agomelatine 25mg depression	escitalopram	nightmares	1 day no change not recovered

Patient A is a female aged 51-60 years years with nightmares following administration of agomelatine 25 mg daily for sleep disorder with a latency of eight days. In addition to nightmares the patient experienced distal paraesthesias, abdominal cramps, sleep walking, nausea, fear and she was hard to awaken. It is not known whether agomelatine was withdrawn or continued, and the outcome is unknown.

Patient B is a male aged 71 years and older with nightmares following administration of agomelatine (daily dose unknown) for depression with a latency of two days. Agomelatine was withdrawn and the patient recovered.

Patient C is a female aged 41-50 years with nightmares and dizziness following administration of agomelatine 25mg daily for depression with a latency of five days. The dose of agomelatine was not changed and the outcome is unknown.

Patient D is a female aged 31-40 years with nightmares following administration of agomelatine 25mg daily for depression with a latency of one day. During the three weeks she had been using agomelatine, she experienced nightmares every night except for one. Agomelatine was continued and the patient has not recovered. Prior to the start of agomelatine she had never experienced nightmares. In addition to the nightmares she experienced drowsiness, sweating, headache and trembling fingers of her right hand. All these complaints however, were not as inconvenient as the nightmares. Concomitant medication was escitalopram.

#### Other sources of information regarding nightmares associated with agomelatine use

##### SmPC

The SmPC of Valdoxan® does not contain any information regarding nightmares, however, anxiety is mentioned as a common ADR.

### *Literature*

Although the SmPC describes effects on sleep related processes while using agomelatine, such as the induction of a phase advance of sleep, decline of body temperature and onset of melatonin, no reports of nightmares or abnormal dreaming could be found in publicly available literature sources.

### *Databases*

As described above, the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of nightmares associated with the use of agomelatine, which was reported disproportionately (ROR = 22.4, 95% CI: 7.9 - 63.1).

On March 23<sup>rd</sup>, 2011, the WHO database of the Uppsala Monitoring Centre contained 13 reports of nightmares, concerning nine females and three males. In one case, the sex of the patient involved was not reported. The median age of the patients was 52.5 years (range 27 - 72). The association was disproportionately present in the database (ROR = 15.0, 95% CI: 8.6 – 26.0). In seven cases a positive dechallenge was reported and in one of these there was also a positive rechallenge.

On March 23<sup>rd</sup>, 2011, the Eudravigilance database contained ten reports of nightmares associated with the use of agomelatine which was reported disproportionately (ROR = 13.8, 95% CI: 7.3 - 25.8). It concerns seven females and two males. In one case, the sex of the patient involved was not reported. The median age of the patients was 55.5 years (range 28 - 72). Six reports were classified as 'serious', the criterion for seriousness being 'hospitalisation' in one case. For the remaining five serious cases, the criterion for seriousness was 'medically relevant'.

### *Mechanism*

Although the mechanism of agomelatine-induced nightmares remains unclear, there is some knowledge regarding sleep physiology that can provide some insights.

As described above, agomelatine is both a MT1 / MT2 receptor agonist and a 5-HT<sub>2C</sub> receptor antagonist. The antagonistic effect on the 5-HT<sub>2C</sub> receptor results in release of dopamine in the frontal cortex of the brain, and dopamine receptor stimulation is thought to be a common mechanism of drug-induced nightmares [5].

In addition it is known that nightmares occur primarily during the last stages of REM sleep and that drugs suppressing REM sleep should be considered in the etiology of nightmares [5]. However, a study investigating the sleep EEG in patients using agomelatine showed no influence on REM sleep latency, the amount of REM sleep, or REM density during sleep [6].

## **Discussion and conclusion**

The aim of this report was to give an overview of the ADRs associated with the use of agomelatine, using information from the spontaneous reporting system. Spontaneous reporting is based on concerned reporting i.e when a health professional or patient see an ADR which they find worrying, they will report it. The chance of receiving reports with rare and serious ADRs through spontaneous reporting is therefore relatively high.

The overall safety profile presented in this report is rather consistent with the information provided in the SmPC of agomelatine. When analyzing the data, a new possible signal for agomelatine and nightmares has been identified.

#### References

1. European SPC Valdoxan® (agomelatine). (version date: 3-2-2011, access date: [http://www.ema.europa.eu/docs/nl\\_NL/document\\_library/EPAR\\_-\\_Product\\_Information/human/000915/WC500046227.pdf](http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000915/WC500046227.pdf)).
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6. Quera Salva MA, Vanier B, Laredo J, Hartley S, Chapotot F, Moulin C, Lofaso F, Guilleminault C. Major depressive disorder, sleep EEG and agomelatine: an open-label study. Int J Neuropsychopharmacol. 2007;10(5):691-6.

This signal has been raised on July 2011. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB [www.cbgmeb.nl/cbg/en/default.htm](http://www.cbgmeb.nl/cbg/en/default.htm) or the responsible marketing authorization holder(s).

*Information from the Marketing Authorisation Holder: The updated SmPC was approved on 17/07/11 and includes 'nightmares' in section 4.8.*