Signal

# Agomelatine and Increased Blood Pressure

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## Summary

Agomelatine is a non-selective melatonin receptor MT1 and MT2 agonist plus a neutral serotonergic 5-$HT_{2C}$ antagonist indicated for the treatment of major depressive episodes. Of the 24 reports from eight countries on increased blood pressure and agomelatine in the WHO global database of individual case safety reports (VigiBase), twelve were eligible for assessment. Of these, six revealed a consistent pattern of a short time to onset and nine reported recovery on dechallenge, with a positive rechallenge in two of them. Although data on the mechanism of action of agomelatine, as well as a former signal, suggest a mild hypo- rather than hypertensive action, it is also true that melatonin, which is structurally closely related to agomelatine, has hypertension as a labelled adverse effect. Thus, despite the presence of additional risk factors for hypertension in a considerable proportion of these cases, a contributory role of agomelatine to the events cannot be excluded.

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## Introduction

Agomelatine has been authorised in the European Union and other countries for the treatment of major depressive episodes. It has not been authorised in the USA. Agomelatine is a potent, non-selective melatonin receptor MT1 and MT2 agonist plus a neutral serotonergic 5-$HT_{2C}$ antagonist. Synergy between the two types of receptors has been hypothesized as accounting for its mode of action. Inhibition of the 5-$HT_{2C}$ receptor is held responsible for the direct antidepressant effect. Unlike other antidepressants that often trigger sleep disorders the advantage of agomelatine is that it has a beneficial effect on sleep.[1-3]

Agomelatine is indicated for adults (over 18 years) because of the lack of data in paediatric populations. The recommended dose is 25 to 50 mg daily taken orally at bedtime. Its safety profile requires regular monitoring of liver function in all patients before and during treatment. Agomelatine is metabolised mainly by CYP1A2 (90%) and CYP2C9/19 (10%). Consequently, drugs that interact with these isoenzymes may interact with agomelatine.[4]

Normal blood pressure (BP) varies with age and is influenced by various factors such as cardiac output, vascular resistance and venous return and pressure; any change in these variables can lead to fluctuations in BP. Thus, there is no absolute threshold to define "normal BP". In general, patients are taught that 120/80 (systolic/diastolic in mmHg) is taken as "normal", 130/85 as "high normal", then higher values as different stages of hypertension. However, these values vary with age (e.g. the normal values are 117/77 and 134/87 mmHg between 14 to 19, and 60 to 64 years, respectively).[5]

Twenty-four reports have been observed in the WHO global database of individual case safety reports (ICSRs), VigiBase, for blood pressure increased (BPI) under agomelatine treatment.

## Reports in VigiBase

On 14 April 2019, 24 reports were retrieved from VigiBase for BPI following agomelatine administration (Table 1). The adverse events occurred between December 2012 and November 2017. The ICSRs originated from eight countries: Germany (15 cases), Austria (2), Switzerland (2), and Australia, the Czech Republic, Portugal, South Africa, and Turkey (one each). They were spontaneous reports except cases 2 and 21 which came from clinical studies. The reporters were physicians with the exception of cases 1 and 16 (non-health-care professionals), 12 (pharmacist), as well as 10 and 20 (other healthcare professionals), while in case 11 the reporter was unknown. In cases 3, 7 and 14 the outcome was not reported, otherwise, except in cases 11 and 16, the patients recovered. In the reports agomelatine was the only suspected drug, except case 9 where all those administered except esomeprazole were reported as suspected. In 14 cases where the increased blood pressure values were also reported, they varied considerably.

The cases in Table 1 were analysed first to exclude those where the concomitant medication could cause BPI/hypertension. The European product information of the concomitant drugs (European Medicines Agency webpage or the MRI product index[6]) revealed that, in addition to typical antidepressants (trazodone, paroxetine, venlafaxine, sertraline and clomipramine), pregabalin (used, among others, in cases of generalised anxiety) and ezetimibe (primary hypercholesterinaemia) have hypertension labelled as an adverse effect. Thus, cases 3, 4, 9 and 13 were not used for the initial review. (In cases 8, 21 and 23, paroxetine or clomipramine were indicated as concomitant drugs, however, their administration was discontinued before agomelatine was started, and the BPI occurred days later, so these cases were included.)

During the next "filtering", the following cases were excluded: cases 2, 5 and 8 (one and a half months, two years and nine months agomelatine treatment before the onset of BPI, respectively), case 7 (poor reporting), case 10 (according to its narrative, the agomelatine treatment was maintained, but the patient's BP improved), case 14 (onset of BPI reported on the day of the agomelatine administration, then the treatment was continued with no further data), case 15 (it was a suicide attempt, taking among others, 1050 mg agomelatine with no BPI first then 150/90 mmHg value later, but the patient had a mild hypertension), and case 22 as the patient had an underlying hypertension and, according to the narrative, a reduction of the antihypertensive treatment was made at the time of agomelatine initiation.

Thus, only 12 ICSRs (cases 1, 6, 11, 12, 16-21, 23 and 24) remained for detailed analysis.

Well-controlled arterial hypertension/hypertension as one of the patients' underlying diseases was reported in cases 17-20 and 24. The reported time to onset of the increased blood pressure was a few hours in case 17, three days in case 23, about seven days in cases 12 and 21, while general statements (such as "after introduction" or "initiation", "since she took it") indicated that the time to onset seemed to be short (in cases 1, 16, 20, 24). In case 18 the BPI happened "after the dose was increased from 25 mg to 50 mg". In nine cases (1, 6, 12, 17, 19, 20, 21, 23 and 24) positive dechallenge (plus in case 18 reaction abated for dose reduction) while in two cases (1, 12) positive rechallenge were reported. It should also be stressed that labelled adverse effects of agomelatine (e.g. migraine, nausea, sweats, anxiety, restlessness, insomnia, dizziness and blurred vision), if they occurred in the analysed cases, also abated at the same time as BPI did (cases 19-21 in Table 1). In case 12 increased heart rate abated together with BPI while the outcome of other events labelled for agomelatine (tiredness, somnolence and headache) was not reported.

It should be noted that 17 reports for hypertension following agomelatine administration were also found in VigiBase (13 October 2019). In six of them no concomitant medication was reported and in six other cases, although there was concomitant medication, agomelatine was reported as the only suspect drug. (Only two of these latter six cases also reported concomitant medications which have hypertension as a labelled ADR, i.e. allopurinol and sertraline.) In four cases positive dechallenge also occurred. The time to onset, when it could be identified from the reports, varied from "same day" (three cases) to two days (two cases), and around two weeks (two cases) up to one month or longer (seven cases). Labelled adverse effects of agomelatine occurred and abated together with the hypertension in ten cases. Although these "agomelatine and hypertension" reports were not combined with the "agomelatine and BPI" ones, they seem to be in line with the latter and strengthen the results of this analysis.

## Literature and labelling

Hypertension/BPI is not listed in the European Summary of Product Characteristics of agomelatine. Furthermore, it states that "agomelatine had neutral effect on heart rate and blood pressure in clinical trials".[4] (There were clinical trials where hypertension was reported in the agomelatine arm. Its frequency was found to be 1.2%[7] but because of the limited number of the subjects involved and the lack of a placebo arm in this trial, the causality could not be established.)

It is also well-known that people suffering from depression are more likely than the others to develop hypertension.[8]

Experiments have suggested that agomelatine prevents rather than causes hypertension.[9] Moreover, in 2014, the Uppsala Monitoring Centre published a signal on hypotension occurring under agomelatine treatment. In response to the signal the marketing authorisation holder accepted that 5-$HT_{2C}$/5-$HT_{2B}$ antagonists could induce an antihypertensive effect in animals and/or humans with hypertension, while it did not endorse it as a clinically relevant safety concern.[10]

Melatonin, structurally closely related to agomelatine but binding to the MT receptors exclusively is used for sleep disorders such as short-term primary insomnia or to decrease jet-lag.[11] It is interesting that clinical studies revealed that its use at night an hour before sleep appeared to lower BP. (There is some debate about its mechanism: is it based on serotonin antagonism by melatonin or is it because the subjects had fuller, better quality sleep?)[11, 12] On the other hand, melatonin has hypertension as a labelled adverse effect[13, 14] with a frequency of "uncommon" (that means 0.1 to 1.0%).[13]

It is also well-known that some medicines that usually lower blood pressure may paradoxically increase blood pressure.[14] There are drugs (such as pregabalin, indicated, among others, to generalised anxiety disorders) that have labelled adverse reactions both hypo- and hypertension with the same frequency.[15]

## Discussion and conclusion

Based on the overall reporting of adverse reactions for agomelatine and of the adverse reaction BPI in VigiBase as a whole, the expected value for the number of reports of the combination is 16 and the $IC_{025}$ is negative (as of 27 June 2019). However, agomelatine is not used in the USA where BPI is more commonly reported overall, and in a

disproportionality analysis adjusted for region of origin, the expected value is around 10, rendering a stronger statistical association which would be highlighted as disproportionally reported by IC analysis. This means that if its calculation is restricted to the rest of the world (non-US reports), the $IC_{025}$ is positive. Moreover, taking the high number of positive dechallenges in the analysed ICSRs into account (where labelled adverse effects of agomelatine abated together with the BPI) and the positive (in one case double) rechallenges, they strongly suggest a positive causal relationship.

The BPI action of agomelatine might be dose-dependent (it occurred only at higher doses in one case and the patient who experienced repeated rechallenges was a slow CYP metaboliser). Moreover, the fact that the individual variability of the absolute bioavailability of agomelatine is substantial[4] might explain its rare and sporadic occurrence.

Considering also the mild hypotensive action of agomelatine and the preceding signal on agomelatine – hypotension,[10] where the number of positive dechallenges were also high with one positive rechallenge, the former statement may be extended to agomelatine – change in BP (both hypo- and hypertension). The paradoxical action of certain antihypertensives causing BPI may be explained by an impaired BP regulation system that "over-reacts" to the stimulus. Indeed, five patients of the analysed 12 ICSRs (in cases 17-20 and 24) had reported "well-controlled" hypertension (i.e. an underlying disease where the BP regulation was impaired).

The marketing authorisation holder's statements in certain ICSR narratives that the cases do not trigger any changes in the core data sheet are fully agreed upon, the reaction is far from being proven and can be extremely rare. However, a signal only means information on a possible causal relationship between an adverse event and a drug. Considering the above-mentioned aspects, in conclusion, agomelatine and BPI (perhaps also more widely: agomelatine and change in BP) is considered a signal.

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**Table 1. Overview of reports in VigiBase of blood pressure increased in association with agomelatine.**

| Case | Sex, age | Underlying disease | Agomelatine dose, treatment duration | Concomitant drugs | Reported reactions | De/Rechallenge |
|---|---|---|---|---|---|---|
| 1 | M, 74 | Coronary by-pass, insomnia | 25 mg/d, not specified (within 1 month) | nebivolol, lercanidipine, tamsulosin, finasteride, diazepam | BPI, tachycardia, muscle cramps | Positive dechallenge, positive rechallenge |
| 2 | F, 72 | Hypertension, depression, obesity | 25 mg/d, 1.5 m | | BPI, nausea | |
| 3 | F, 58 | Depression, hypertension, sleep disorder | 25 mg/d, 18 d | lorazepam, trazodone | BPI, dizziness, heart rate increased, Nausea | |
| 4 | M, 72 | Depression, BPH, glaucoma, hyper-cholesteremia. arterial hypertension, insomnia, obesity, sleep apnoea syndrome, gonarthrosis | 50 mg/d, 2 m | telmisartan, ezetimibe, dorzolamide, simvastatin | BPI, alanine aminotransferase, aspartate aminotransferase and gamma-glutamiltransferase increased | positive dechallenge (all events) |
| 5 | F, 63 | Depression, arterial hypertension, obesity | 25 mg, 2 y | losartan | BPI, sinus tachycardia | |
| 6 | M, 52 | Depression, somatization disorder | 25 mg | | BPI | positive dechallenge |
| 7 | | | | | BPI | |
| 8 | M, 31 | Depression (cousin psychiatric) | 25 mg/d, 9 m | hyoscine, medazepam, paroxetine | BPI, suicidal and homicidal ideation, nervousness, anger, aggression, impaired driving ability | positive dechallenge (all events unspecified) |
| 9 | M, 53 | Recurrent depression, generalised anxiety disorders | | bisoprolol, clonazepam, pregabalin, venlafaxine, mirtazapine (all also suspected drugs), esomeprazole | BPI, vertigo, aggression aggravated, fall, gait instability, tension | |
| 10 | F, 61 | Sleep disturbance, pain in spine, bronchitis, prolapsed disc nos | 25 mg/d, (onset 14 d) | trolnitrate, valsartan, budesonide/ formoterol, levothyroxine, lidocaine, zolpidem | BPI, transient ischemic attack, paraesthesia, muscle tension, insomnia | Agomelatine maintained, BPI recovered |
| 11 | F, 59 | | 7 d | flecainide, warfarin, atorvastatin | BPI, drug interaction | |

| Case | Sex, age | Underlying disease | Agomelatine dose, treatment duration | Concomitant drugs | Reported reactions | De/Rechallenge |
|---|---|---|---|---|---|---|
| 12 | F, cca 30 | Depression | 25 mg/d cca 1w | escitalopram, ethyl loflazepate, alprazolam, salbutamol | BPI, increased heart rate, tiredness, somnolence, headache | positive dechallenge, positive rechallenge (BPI and heart rate) |
| 13 | M, 61 | Depression, insomnia | 25 mg/d | sertraline | BPI, tachycardia, palpitations | positive dechallenge, positive rechallenge |
| 14 | M, 18 | Depression | 25 mg/d, 0 d | | | |
| 15 | F, 63 | Depression, arterial hypertension, chronic alcohol abuse, suicide attempt | 1050 mg (suicidal intention), 1 d | mirtazapine, lercanidipine | BPI, increased alkaline phosphatase, AST and bilirubin and blood glucose and C-reactive protein and creatinine and LDH and GGT, aspiration, high creatine kinase and uric acid, febrile reaction, hypokalaemia, nervousness, tachycardia, unrest | |
| 16 | F, 54 | Depression, Hashimoto's disease, hypometabolism (CYP2 d6 and c19 slow metaboliser) | 25 mg/d, 1 m<br>6.25 mg/d, 17 d<br>12.5 mg/d, 4 m<br>the drug was withdrawn for a period of time between the different dosage regimens. BPI occurred after reintroducing it at dose 12.5 mg | levothyroxine | BPI, anxiety, insomnia, hot flushes facial, migraine, nausea, sweats, generalised hot feeling, blue-red colouration of the skin | |
| 17 | M, 74 | Depression, coronary heart disease, arterial hypertension, diabetes mellitus type 2 | 25 mg/d, 1 d | trimipramine, glyceryl | BPI, restlessness, nocturnal awakening | positive dechallenge |
| 18 | F, 54 | Depression, hypertension | 50 mg/d<br>25 mg/d<br>Patient started on 25 mg, the dose was then increased to 50 mg and the patient experienced BPI | antihypertensives | BPI, red face | dose reduced to 25 mg/d and BPI recovered |

| Case | Sex, age | Underlying disease | Agomelatine dose, treatment duration | Concomitant drugs | Reported reactions | De/Rechallenge |
|---|---|---|---|---|---|---|
| 19 | ?, ? | Sleep disorder, hypertension, reflux esophagitis, left bundle branch block | 25 mg/d, 11 d | lercanidipine (1 y), esomeprazole | BPI, new left bundle branch block, chest pain, dizziness, blurred vision | positive dechallenge (all) |
| 20 | F, over 70 | Depression, GI inflammation viral, hypertension, irritable bowel, panic attacks, sleep disorder, bowel cancer removed, cerebral disorder, anxiety disorder | 50 mg/d, around 1 m (onset: "since she took agomelatine") | ciprofloxacin, HCT/ olmesartan | BPI, blurred vision, head pressure, noises in head, stiff neck, anxiety aggravated, contraindicated drug administered | positive dechallenge (all) |
| 21 | F, 39 | Recurrent depressive disorder | 25 mg/d, 18 d | opipramol, paroxetine | BPI, aggressive behaviour, dizziness, excitement, mood swings, suicidal ideation, unrest | positive dechallenge (all) |
| 22 | M, 45 | Insomnia, hypertension | 25 mg/d, 4 d, then 50 mg/d, about 2 w | bisoprolol | BPI, shaking of hands, feeling irritated, panic attacks, nausea, dizziness, sweating | BPI abated when amlodipine was taken |
| 23 | M, 71 | Depression, Parkinson's disease | 25 mg/d, 7 d | benserazide, levodopa, clomipramine | BPI | positive dechallenge |
| 24 | F, 44 | Anxiodepressive syndrome, hypertension, post-concussion syndrome | 25 mg/d, 10 d | escitalopram, pantoprazole, ramipril | BPI, headache | positive dechallenge |

BPI = blood pressure increased, d = day, w = week, y = year, BPH = benign prostatic hyperplasia, HCT = hydrochlorothiazide

## SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

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## Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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# Caveat Document

**Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs)**. Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

**Tentative and variable nature of the data**

*Uncertainty:* The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

*Variability of source:* Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

*Contingent influences:* The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

*No prevalence data:* No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

*Time to VigiBase:* Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

**For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.**

**Prohibited use of VigiBase Data includes, but is not limited to:**

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

**Any publication, in whole or in part, of information obtained from VigiBase must include a statement:**

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

**Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.**

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.



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