**Drug Review**

Agomelatine: A New Antidepressant with a Novel Mechanism of Action

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**Introduction**

Major depressive disorder (MDD) is a prevalent, chronic illness and one of the leading causes of disability worldwide. MDD is among the most incapacitating conditions in the world. Estimated lifetime prevalence of MDD is 16.6% and the one year prevalence is 6.7%. MDD is associated with significant personal, societal, and economic burden and therefore merits effective & focused treatment strategies. Unfortunately, treatments for depression are far from ideal, and often inadequate. Fewer than 50% of patients with depression achieve full remission with optimized treatments. Despite the increase in the available therapeutic armamentarium (Kasper et al. 1994), in particular selective serotonin (5-HT) reuptake inhibitors (SSRIs) and serotonin-nor adrenaline (NA) reuptake inhibitors (SNRIs), 50% of depressed patients remain untreated. In addition to the need to administer the drugs for weeks or months before seeing clinical benefit, side effects are still a serious problem even with the newer medications. A substantial number of patients discontinue antidepressant treatment during the first few weeks of treatment, and poor compliance remains one of the most common obstacles of antidepressant treatment (Zajecka 2000). The SSRIs are relatively well tolerated compared with tricyclic, imipramine-type, antidepressants, but they also cause some adverse effects linked to their actions on gastrointestinal tract, sexual functioning and sleep patterns (Vida and Looper 1999). A withdrawal syndrome on stopping treatment has also been reported with the use of some SSRIs (Montgomery et al. 2004).

There is still a great need for faster acting, safer and better tolerated and more effective treatments for depression, as such treatments could lead to more complete remission in more patients (Moller 2008). There is now an accumulation of knowledge derived from animal studies about non-monoamine systems that might contribute to the pathophysiology of depression and human evidence in support of this concept is increasingly available (Baghai et al. 2006). Among the various strategies to help patients with new, more effective and better tolerated treatments, the re-synchronization of biological rhythms appears to be particularly attractive given that a disruption of circadian rhythms is characteristic of a large number of mood disorders (Kasper and Wehr 1992; Winkler et al. 2005).

The present review provides an overview on the available preclinical and clinical data on agomelatine, a new antidepressant with a novel mechanism of action.

**Agomelatine**

Agomelatine is a new antidepressant with selective agonist actions at melatonin receptors and selective antagonist action at serotonin 5HT-2C receptors. It does not affect the uptake of serotonin, nor adrenaline or dopamine.

**Pharmacodynamic properties**

Pharmacotherapeutic group: Other antidepressants, ATC-code: NO6AX22

Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist. Binding studies indicate that agomelatine has no effect on monoamine uptake and no affinity for adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors.

Agomelatine resynchronizes circadian rhythms
in animal models of circadian rhythm disruption. Agomelatine increases nor adrenaline and dopamine release specifically in the frontal cortex and has no influence on the extra cellular levels of serotonin.

Agomelatine has shown an antidepressant-like effect in animal models of depression (learned helplessness test, despair test, chronic mild stress) as well as in models with circadian rhythm desynchronisation and in models related to stress and anxiety.

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

**Pharmacokinetic properties**

**Absorption and bioavailability:**

Agomelatine is rapidly and well (80%) absorbed after oral administration. Absolute bioavailability is low (< 5% at the therapeutical oral dose) and the interindividual variability is substantial. The bioavailability is increased in women compared to men. The bioavailability is increased by intake of oral contraceptives and reduced by smoking. The peak plasma concentration is reached within 1 to 2 hours.

In the therapeutic dose-range, agomelatine systemic exposure increases proportionally with dose. At higher doses, a saturation of the first-pass effect occurs.

Food intake (standard meal or high fat meal) does not modify the bioavailability or the absorption rate. The variability is increased with high fat food.

**Distribution**

Steady state volume of distribution is about 35 l and plasma protein binding is 95% irrespective of the concentration and is not modified with age and in patients with renal impairment but the free fraction is doubled in patients with hepatic impairment.

**Biotransformation**

Following oral administration, agomelatine is rapidly metabolized mainly via hepatic CYP1A2; CYP2C9 and CYP2C19 isoenzymes are also involved but with a low contribution. The major metabolites, hydroxylated and demethylated agomelatine, are not active and are rapidly conjugated and eliminated in the urine.

**Elimination**

Elimination is rapid, the mean plasma half-life is between 1 and 2 hours and the clearance is high (about 1,100 ml/min) and essentially metabolic. Excretion is mainly (80%) urinary and in the form of metabolites, whereas unchanged compound recovery in urine is negligible. Kinetics is not modified after repeated administration.

**Renal impairment**

No relevant modification of pharmacokinetic parameters in patients with severe renal impairment has been observed (n=8, single dose of 25 mg), but caution should be exercised in patients with severe or moderate renal impairment as only limited clinical data are available in these patients.

**Hepatic impairment**

In a specific study involving cirrhotic patients with chronic mild (Child-Pugh type A) or moderate (Child-Pugh type B) liver impairment, exposure to agomelatine 25 mg was substantially increased (70-times and 140-times, respectively), compared to matched volunteers (age, weight and smoking habit) with no liver failure.

**Ethnic groups**

There is no data on the influence of race on agomelatine pharmacokinetics.

**Preclinical safety data**

In mice, rats and monkeys sedative effects were observed after single and repeated administration at high doses. In rodents, a marked induction of CYP2B and a moderate induction of CYP1A and CYP3A were seen from 125 mg/kg/day whereas in monkeys the induction was slight for CYP2B and CYP3A at 375 mg/kg/day. No hepatotoxicity was observed in rodents and monkeys in the repeat dose toxicity studies.

Agomelatine passes into the placenta and fetuses of pregnant rats. Reproduction studies in the rat and the rabbit showed no effect of agomelatine on fertility, embryofoetal development and pre- and post natal development. A battery of in vitro and in vivo standard genotoxicity assays concludes to no mutagenic or clastogenic potential.
of agomelatine. In carcinogenicity studies, agomelatine induced an increase in the incidence of liver tumors in the rat and the mouse, at a dose at least 110-fold higher than the therapeutic dose. Liver tumors are most likely related to enzyme induction specific to rodents. The frequency of benign mammary fibroadenomas observed in the rat was increased with high exposures (60-fold the exposure at the therapeutic dose) but remains in the range of that of controls. Safety pharmacology studies showed no effect of agomelatine on hERG (human Ether à-go-go Related Gene) current or on dog Purkinje cells action potential. Agomelatine did not show proconvulsive properties at ip doses up to 128 mg/kg in mice and rats.

**Agomelatine: Demonstrated efficacy in acute phase**

Agomelatine’s onset of efficacy has been reported and measured on the Clinical Global Impression-Improvement [CGI-I] scale and Visual Analog Scales [VAS] as early as the first week of treatment. From the first week of treatment, Agomelatine demonstrated to provide significant efficacy in terms of CGI score improvement, as well as VAS score improvement.

**Significant improvement in CGI score at week 1 with agomelatine(Valdoxan)**

In a 6-week randomized, double-blind study conducted in 332 patients with major depressive disorder, agomelatine was demonstrated to provide early onset of antidepressant efficacy as reported by a significant clinical improvement from the first week of treatment on the CGI-I scale (Δ=0.39 in favor of agomelatine 25-50 mg/day compared with venlafaxine IR 75-150 mg/day, P=0.0001).

**Significant improvement in VAS score at week 1 with agomelatine(Valdoxan)**

At 1 week just after initiation in a randomized, double-blind study conducted in 332 patients with major depressive disorder, agomelatine demonstrated on VAS scales a significant improvement versus venlafaxine IR 75-150 mg/day in the sensation of “feeling good” (P<0.001), as well as in “daytime vigilance” and “quality of sleep,” two core symptoms of depression, as early as the first week of treatment.

**Agomelatine: Significant efficacy in the short term**

Agomelatine’s antidepressant efficacy has been demonstrated in a large clinical program including 5 800 patients of whom 3 900 were treated with agomelatine. The short-term efficacy of agomelatine has been demonstrated over treatment periods of 6 to 12 weeks using standardized scales (Hamilton Depression Rating Scale [HAMD], Montgomery and Asberg Depression Rating Scale [MADRS], Clinical Global Impression-Improvement [CGI-I] and Clinical Global Impression-severity [CGI-S] scales) versus placebo and active comparators.

Agomelatine resulted in significant improvements in HAMD scores at week 6 and week 8. Furthermore, agomelatine provided high HAMD response rate at week 6 and high MADRS remission rate at week 12.

**Significant improvement at week 6 with agomelatine(Valdoxan)**

The antidepressant efficacy of agomelatine 25 mg to 50 mg has been demonstrated in a 6-week,
randomized, double-blind, placebo-controlled, parallel-group study in 260 patients with MDD.

After 6 weeks of treatment, the difference in HAMD total score between agomelatine and placebo was 3.44 (P<0.001), with a significant difference from placebo after only two weeks of treatment (P<0.05).

**Significant improvement at week 8 with agomelatine (Valdoxan)**

In a 8-week, dose-finding, double-blind placebo-controlled study conducted in 711 MDD patients, the antidepressant efficacy of agomelatine has been illustrated by a significant difference in mean HAMD final scores in favor of agomelatine 25mg showed (mean difference=2.57 in favor of agomelatine 25 mg/day versus placebo, P<0.05).

**High response rate at week 6 with agomelatine (Valdoxan)**


In a 6-week, randomized double-blind comparative study comparing Valdoxan 25-50 mg/day and venlafaxine IR 75-150 mg/day in 332 MDD patients, 76% of Valdoxan-treated patients were responders after 6 weeks of treatment versus 70.6% in the venlafaxine treatment arm.

**High remission rate at week 12 with agomelatine (Valdoxan)**

In a 12-week, randomized double-blind comparative study comparing Valdoxan 50 mg/day and venlafaxine XR 150 mg/day in 276 MDD patients, 73% of Valdoxan-treated patients were in remission after 12 weeks of treatment versus 66.9% in the venlafaxine treatment arm.

Note: remission was defined as a MADRS total score ≤ 12 at week 12.

Agomelatine: Demonstrated efficacy in maintenance phase

Long-term efficacy of agomelatine (Valdoxan) in prevention of relapses at 6 months

The maintenance of antidepressant efficacy of agomelatine was demonstrated over a treatment period of 6 months in a relapse prevention study. Patients responding to 8/10-weeks of acute treatment with open-label agomelatine 25 to 50 mg once daily were randomized to either agomelatine 25 or 50 mg for 6 months. Study results showed that the incidence over time of patients experiencing relapse is significantly lower with agomelatine compared with placebo (20.6% versus 41.4%; P<0.0001).


Agomelatine: Efficacy in moderate to severe depression

Agomelatine is effective whatever the intensity of depressive symptoms. The efficacy of agomelatine was observed in the more severely depressed patients (baseline HAM-D ≥ 25) in all positive placebo-controlled studies.

Efficacy of Agomelatine (Valdoxan) in severe depression

Results of the meta-analysis of three positive, randomized, double-blind, placebo controlled studies in 357 patients treated with agomelatine and 360 patients treated with placebo show that agomelatine is effective in treating severe depression. In the subgroup of severely depressed patients (defined as HAMD17 ≥ 25 at inclusion), agomelatine was significant superior to placebo with a difference of 3 points on the HAMD17 scale after 6/8 weeks of treatment.

Agomelatine’s antidepressant effect is greater for more severe depression. In patients with a greater baseline score (>30 on HAMD17 scale), the agomelatine-placebo difference was of 4.53 points.


Clinical Particulars

Therapeutic indications

Treatment of major depressive episodes in adults

Posology and method of administration

The recommended dose is 25 mg once daily taken orally at bedtime with or without food.

After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets, taken together at bedtime.

Liver function tests should be performed in all patients: at initiation of treatment, and then periodically after around six weeks (end of acute phase), twelve weeks and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.
Children and adolescents

Agomelatine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

Elderly patients

Efficacy has not been clearly demonstrated in the elderly (≥ 65 years). Only limited clinical data is available on the use of Agomelatine in elderly patients ≥ 65 years old with major depressive episodes.

Patients with renal impairment

Limited clinical data on the use of agomelatine in depressed patients with severe or moderate renal impairment with major depressive episodes is available. Therefore, caution should be exercised when prescribing agomelatine to these patients.

Patients with hepatic impairment

Agomelatine is contraindicated in patients with hepatic impairment

Treatment discontinuation

No dosage tapering is needed on treatment discontinuation.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hepatic impairment (i.e. cirrhosis or active liver disease)

Concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)

Special warnings and precautions for use

Use in children and adolescents

Agomelatine is not recommended in the treatment of depression in patients under 18 years of age since safety and efficacy of agomelatine have not been established in this age group.

Use in elderly patients with dementia

Agomelatine should not be used for the treatment of major depressive episodes in elderly patients with dementia since the safety and efficacy of agomelatine have not been established in these patients.

Mania / Hypomania

Agomelatine should be used with caution in patients with a history of mania or hypomania and should be discontinued if a patient develops manic symptoms.

Suicide/suicidal thoughts

Close supervision of patients at high risk of suicide should be done especially early in treatment and following dose changes.

Caregivers of patients should be alerted to the need to monitor for any clinical worsening, suicidal behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

Combination with CYP1A2 inhibitors

Combination with potent CYP1A2 inhibitors is contraindicated. Caution should be exercised when prescribing agomelatine with moderate CYP1A2 inhibitors (e.g. propranolol, grepafloxacin, enoxacin) which may result in increased exposure of agomelatine.

Increased serum transaminases

Therapy should be discontinued if the increase in serum transaminases exceeds 3X upper limit of normal and liver function tests should be performed regularly until serum transaminases return to normal.

If any patient develops symptoms suggesting hepatic dysfunction liver function tests should be performed. The decision whether to continue the patient on therapy with agomelatine should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed therapy should be discontinued.

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take agomelatine as it contains lactose.

Interaction with other medicinal products and other forms of interaction

Potential interactions affecting agomelatine

Agomelatine is metabolized mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9/19 (10%). Medicinal products that interact with these isoenzymes may decrease or increase the bioavailability of agomelatine.
Fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor markedly inhibits the metabolism of agomelatine resulting in a 60-fold (range 12-412) increase of agomelatine exposure. Consequently, co-administration of agomelatine with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated.

Combination of agomelatine with estrogens (moderate CYP1A2 inhibitors) results in a several fold increased exposure of agomelatine; caution should be exercised when prescribing agomelatine with other moderate CYP1A2 inhibitors (e.g. propranolol, grepafloxacine, enoxacine) until more experience has been gained.

Potential for agomelatine to affect other medicinal products

In vivo, agomelatine does not induce CYP450 isoenzymes. Agomelatine inhibits neither CYP1A2 in vivo nor the other CYP450 in vitro. Therefore, agomelatine will not modify exposure to medicinal products metabolized by CYP 450.

Medicinal products highly bound to plasma protein

Agomelatine does not modify free concentrations of medicinal products highly bound to plasma proteins or vice versa.

Other medicinal products

No evidence of pharmacokinetic or pharmacodynamic interaction with medicinal products which could be prescribed concomitantly with agomelatine in the target population was found in phase I clinical trials: benzodiazepines, lithium, paroxetine, fluconazole and theophylline.

Alcohol

The combination of agomelatine and alcohol is not advisable.

Electroconvulsive therapy (ECT)

Animal studies have not shown proconvulsant properties. Therefore, clinical consequences of ECT concomitant treatment with agomelatine are considered to be unlikely.

Pregnancy and lactation

For agomelatine, no clinical data on exposed pregnancies are available.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embry-onal/foetal development, parturition or postnatal development Caution should be exercised when prescribing to pregnant women.

It is not known whether agomelatine is excreted into human milk. Potential effects of agomelatine on the breast-feeding infant have not been established. If treatment with agomelatine is considered necessary, breastfeeding should be discontinued.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, considering that dizziness and somnolence are common adverse reactions patients should be cautioned about their ability to drive a car or operate machinery.

Undesirable effects

Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse reactions were nausea and dizziness.

These adverse reactions were usually transient and did not generally lead to cessation of therapy.

Adverse reactions are listed below using the following convention: very common (e<1/10); common (e<1/100 to <1/10); uncommon (e<1/1,000 to <1/100); rare (e<1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). The frequencies have not been corrected for placebo.

Nervous system disorders

Common: headache, dizziness, somnolence, insomnia, migraine

Uncommon: paraesthesia

Eye disorders

Uncommon: blurred vision

Gastrointestinal disorders:

Common: nausea, diarrhea, constipation, upper abdominal pain

Skin and subcutaneous tissue disorders

Common: hyperhidrosis

Uncommon: eczema

Rare: erythematous rash

Musculoskeletal and connective tissue disorders

Common: back pain
General disorders and administration site conditions:
Common: fatigue

Hepato-biliary disorders:
Common increases (>3 times the upper limit of the normal range) in ALAT and/or ASAT (i.e. 1.1% on agomelatine 25/50 mg vs. 0.7 % on placebo).
Rare: hepatitis

Psychiatric disorders:
Common: anxiety
Frequency not known: Suicidal thoughts or behaviour

Overdose

There is limited experience with agomelatine overdose. During the clinical development, there were a few reports of agomelatine overdose, taken alone (up to 450 mg) or in combination (up to 525 mg) with other psychotropic medicinal products. Signs and symptoms of overdose were limited and included drowsiness and epigastralgia.

No specific antidotes for agomelatine are known. Management of overdose should consist of treatment of clinical symptoms and routine monitoring. Medical follow-up in a specialized environment is recommended.

Summary

Agomelatine is a novel antidepressant indicated in the treatment of major depressive episodes in adults. The antidepressant efficacy of agomelatine has been confirmed in four trials versus placebo, three over the short term and one over the long term. The antidepressant efficacy of agomelatine is significantly superior to that of placebo, whatever the symptom intensity, including the more severely depressed patients. The recommended dose of Agomelatine is 1 tablet of 25 mg once daily, taken orally at bedtime. After 2 weeks of treatment, if there is no improvement of symptoms, the dose of agomelatine may be increased to 50 mg once daily, i.e., two 25-mg tablets, taken together at bedtime. Transaminase tests should be performed in all patients: at initiation of treatment and then periodically. At treatment cessation, agomelatine has been shown to be free of discontinuation symptoms. Adverse reactions were usually mild or moderate, and occurred within the first 2 weeks of treatment. The most common adverse reactions were nausea and dizziness. These adverse reactions were usually transient, and did not generally lead to cessation of therapy. Specific sexual dysfunction comparative studies with other antidepressants have shown a numerical trend towards significantly less emergent sexual dysfunction with agomelatine. Agomelatine has been found to have a neutral effect on body weight, heart rate, and blood pressure in clinical studies.

Overall, agomelatine has been demonstrated to combine significant antidepressant efficacy resulting from the restoration of circadian rhythms, and favorable tolerability profile. Contraindications to the use of agomelatine include hepatic impairment and concomitant use with potent CYP1A2 inhibitors.

Conclusion

Agomelatine offers an exciting addition to the ever expanding therapeutic armamentarium for major depressive disorders (MDD). It has a novel mechanism of action characterized by a strong agonist activity at melatonergic receptors and antagonistic activity at 5-HT2C receptors. Agomelatine provides MDD patients with a significant symptomatic relief, as demonstrated by well-documented improvements in depressed mood, anxiety symptoms, and also sleep-wake disturbances (daytime impairment and sleep disturbances). The drug has been shown to effectively treat MDD patients with a particularly robust efficacy in more severely depressed subgroups. Agomelatine may also improve sexual dysfunction. It is well tolerated with a low adverse effect burden, which is reassuring for a drug with a novel mechanism of action. The good safety profile of agomelatine, due to its unique receptor profile, predicts a higher patient acceptability and a better compliance. To summarize, available data on agomelatine makes this novel compound a very promising antidepressant for the near future.

References