

# First-in-class agent heralds new era in depression management

Tuesday, 23 August 2011: Servier Laboratories has launched its new first-in-class agent for the treatment of adult patients with major depression, agomelatine (Valdoxane).

The discovery of the relationship between disturbed circadian rhythms and depression resulted in research into a completely new approach to treating it. A new treatment based on this approach represents the start of a new era in antidepressant therapy, offering hope to the thousands of patients worldwide who suffer from major depression and fail to respond or respond only partially to current treatment options.

The first melatonergic antidepressant, agomelatine synchronises circadian rhythms to treat depression effectively. It is also the first approved agent to incorporate a non-monoaminergic mechanism.<sup>1</sup>

Over the past 50 years, data have shown that patients with depression experience a wide range of circadian rhythm disturbances and that chronotherapeutic interventions can achieve remission of symptoms. A large body of evidence now suggests that clinical depression is a much more complicated syndrome than was previously thought, fed by multiple physiological pathways as well as environmental and social cues.<sup>2</sup> Data showing the correlation between circadian misalignment and depression severity in humans, as well as a large body of evidence in animal models and genetic studies, support the hypothesis that circadian pathways are directly implicated in the pathophysiology of depression and other mood disorders.<sup>2,3</sup>

According to Pretoria based psychiatrist, Dr Franco Colin: "Despite our having many options available for the treatment of depression, many patients either do not respond to current therapies or fail to respond completely. As we've become more aware of the greater complexity of the condition, we've realised that it needs to be addressed in a more comprehensive manner than is possible with the neurotransmitter-focused options currently available. Agomelatine's mode of action and antidepressant efficacy therefore offer an exciting new approach."

Agomelatine is both a melatonergic receptor agonist and a selective 5HT<sub>2c</sub> receptor antagonist.<sup>1,2</sup> "That it works simultaneously and synergistically on both receptors is a key factor in its efficacy," continues Dr Colin. "Targeting them individually does not produce the same results." These two mechanisms work together to resynchronise circadian rhythms and, as a secondary consequence of 5HT<sub>2c</sub> inhibition, indirectly result in an increase in dopamine and noradrenaline in the prefrontal cortex. Agomelatine is not a re-uptake inhibitor.<sup>1</sup>

For decades, treatments available for depression had remained similar, acting through monoaminergic mechanisms with advances that were valuable, but were essentially variations of the same theme.<sup>1</sup> The selective serotonin and noradrenaline reuptake inhibitors (SSRIs and SNRIs), while safer than the earlier tricyclic antidepressants and monoamine oxidase inhibitors in respect of side effects, offered no real gain in efficacy.<sup>1</sup> "The discovery of a link between depression and circadian rhythms and therefore the potential to approach depression via a completely new, yet recognised pathway, could change the face of depression and its treatment," says Dr Colin.

He cautions, however, that agomelatine's action on melatonergic receptors does not make it equivalent to melatonin. "Melatonin is not a treatment for depression, and combining it with an older antidepressant will not duplicate the effects of agomelatine; neither should agomelatine be prescribed solely for sleep disturbances in the absence of diagnosed depression."

Agomelatine is effective against core symptoms of depression, including depressed mood, psychomotor retardation, feelings of guilt, sleep disturbances and daytime fatigue.<sup>4,5</sup> Patients treated with agomelatine reported improvement from as early as the first week of

treatment in respect of symptoms like daytime alertness and quality of sleep.<sup>5</sup> "Agomelatine is associated with improved alertness, better sleep architecture and enhanced daytime functioning," says Dr Colin.

The drug's efficacy has been validated relative to placebo and SSRIs and SNRIs using the 17-item Hamilton Rating Score for Depression (HAM-D17) total score scale, among others.<sup>6,7</sup> Especially noteworthy is that an increased treatment effect has been noted relative to the increased severity of depression.<sup>10</sup> In addition, agomelatine shows promise for the treatment of anxiety<sup>8</sup>, which is a frequent comorbidity in depressed patients<sup>1</sup> and new data suggest that a lack of an emotional blunting effect with agomelatine<sup>11</sup> could positively impact the quality of patients' emotional recovery and ultimately the quality of remission achieved.

According to Dr Colin, agomelatine has a superior side-effect profile which has positive implications for treatment adherence. "It's generally well tolerated and the associated headaches and nausea/vomiting are mild and transient. There is a very slight risk of reversible liver transaminase elevation, but this was only observed in around 1% of trial subjects." Liver function monitoring is therefore recommended in all patients started on agomelatine.<sup>13,14</sup>

The simple dosing regimen – one 25mg tablet taken at bedtime<sup>13,14</sup> – is another key factor in enhancing adherence. The timing of the dose is crucial for the efficacy of this new approach. It has to coincide with the heightened expression of both melatonergic and 5HT<sub>2c</sub> receptors in the SCN (master clock) in the brain.

Extensive international clinical trials involving more than 5 800 adult patients have established both the short- and long-term efficacy of agomelatine in major depression<sup>13</sup>, with associated improvements in sleep quality<sup>5</sup>, preservation of sexual functioning<sup>1</sup> and an absence of weight gain.<sup>1</sup> Moreover, discontinuation is not associated with any withdrawal symptoms.<sup>13,14</sup> Overall, the clinical profile of agomelatine compares favourably to currently available antidepressants and should encourage adherence throughout the treatment period – six months or longer – recommended for durable improvement of a major depressive episode.<sup>1</sup> It has also been proven to reduce significantly the risk of relapse over the long term.<sup>12</sup>

"Agomelatine offers new hope for depressed patients. Its novel mechanism of action gives patients a better chance of a more complete recovery, embracing all elements of depression, including its emotional, cognitive and social aspects," says Dr Colin.

Valdoxane is a schedule 5 medication in South Africa.

## References

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