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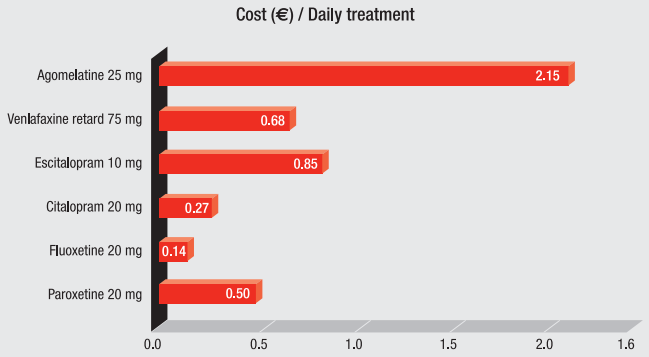
# Agomelatine▲ (Valdoxan®)

## Worse than first-line antidepressants, up to 15-fold more expensive, and a worrying hepatic safety profile


- No clinical trial has been undertaken to compare the antidepressant agomelatine with other antidepressants.
- Clinical trials comparing agomelatine with plcebo have presented discordant results on its efficacy with doubtful clinical relevance.
- At recommended doses (25 mg daily) the agent seems less effective than other antidepressants, while at maximum doses (50 mg daily) no greater efficacy has been shown.
- Its safety profile differs from other antidepressants, with possible dose-dependent liver toxicity.
- The risk-benefit relation of this drug remains unclear.

### Therapeutic indications

Treatment of major depressive disorder in adults.

### Mechanism of action and pharmacokinetics[1]

This drug is an agonist of melatonin receptors and also acts as a 5-HT2c serotonin receptor antagonist, that increases the release of dopamine and noradrenaline, especially in the frontal cortex. Its absolute bioavailability is low (<5%) with a high interindividual variability. Binding with plasmatic proteins is high (95%). It is metabolized in the liver, mainly through the CYP1A2 isoenzyme (90%) and the CYP2C9 and CYP2C19 isoforms (10%). Metabolites are excreted through the kidneys and the agents half life is 1-2 hours.

*There are serious doubts concerning its efficacy, it has safety problems and is more expensive than first line antidepressants.*

### Posology and administration[1]

The recommended oral dose is 25 mg daily before going to bed. If after 2 weeks there is no improvement in symptoms, then the dose may be increased to 50 mg daily. Two 25 mg tablets should be taken before going to bed at night. Progressive reduction in dose is not necessary when interruption of treatment is indicated.

### Clinical efficacy

There are no short and long-term studies published that sufficiently demonstrate the efficacy of this agent when compared to any other antidepresant employed in the treatment of major depressive disorder.

With regard to **short-term studies**, there are seven controlled clinical trials compar-

*The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.*

ing the agent vs **placebo**[6], one dose-finding study[2], two trials comparing it with placebo with no comparison with an active antidepressant[3,4], one in an elderly population and and three at fixed doses, including a branch with active control (fluoxetine or paroxetine). The last four studies were not published but are included in a report by the EMEA[6]. The duration of these studies was 6 weeks, except for the dose finding study which was 8 weeks. The doses of agomelatine vary between 1 and 50mg. The primary endpoint in efficacy employed was the reduction in total score of a standard questionnaire (Hamilton Rating Scale for depression- HAM-D17). Patients included with depression had a HAM-D17 score of ≥ 22.

In the dose finding study[2] only the 25 mg daily oral dose showed greater efficacy when compared to placebo, but was no longer statistically significant when an evaluation was performed of the patients who completed the study. In two trials, administering flexible doses between 25-50 mg of agomelatine, there were differences when compared to placebo of 2.4 points in one[3] and 3.18 points in the other[4].

In the other four unpublished trials, agomelatine at 25 mg daily was not more effective than placebo. In one of them there was no difference between placebo neither in intention to treat or by protocol, and on the contrary, the active control (fluoxetine 20 mg) was superior than placebo. With regard to the other 3 trials, no conclusions could be drawn given that the active controls (fluoxetine 20 mg and paroxetine 20 mg) did not show any differences when compared to placebo[6].

One unpublished trial[6] was carried out to study whether an increase in dose from 25 mg to 50 mg daily would improve efficacy. No statistically significant differences were found when compared to placebo, which put into doubt the additional benefit obtained by incresing the daily dose. Neither were there significant differences found when compared to placebo in the trial carried out in elderly population. Therefore efficacy in the elderly has not been demonstrated[6].

On the whole, the difference between agomelatine and placebo is 1.5 points (95% CI 0.80 - 2.22) in the HAM-D scale. According to the EMEA, the clinical relevance is therefore doubtful (relevance considered when there is a difference in HAM-D scale of 3.5 points) and the magnitude of the antidepressive effect in the short-term seems lower than ISRS antidepressants[6].

With regard to the **long-term** performance of the drug in the prevention of relapses, the results of the trials compared to **placebo** are divergent and the magnitude of the effect has only a marginal clinical relevance[6,9].

## Adverse reactions[1,6]

In short-term studies the incidence of adverse effects was similar to those produced with placebo. The most frequent adverse reactions (≥ 2%) included: headache, nausea, dizziness, dry mouth, diarrhoea, sleepiness, fatigue, abdominal pain, flu-like symptoms and anxiety.

**Liver Function**[1,6]**:** Increments in liver transaminase enzymes have been detected when doses were three times higher than normal levels. These increments are normalised when treatment is discontinued, though severe complications including hepatitis have been described. Liver enzyme determination should be carried out at the onset of treatment and periodically after 6, 12 and 24 weeks and whenever any clinical situation warrants it.

When an increase in transaminases is detected, controls should be repeated within the next 48 hours. Treatment should be interrupted if transminase levels exceed 3 times the upper limit of the normal range and should be controlled until normal levels are recuperated. Treatment should be discontinued in cases of ictericia. Precaution should also be taken when patients drink considerable amounts of alcohol or are under treatment with other drugs with potential liver toxicity.

## Contraindications and precautions[1]

This drug is contraindicated in cases of liver impairment, when there is concomitant use of potent inhibitors of the CYP1A2 (fluvoxamine, ciprofloxacin) and if there exists hypersensitivity to the principal substance or any of the excipients (contains lactose).

Precaution should be taken when the patient is going to drive or operate machinery or in patients under treatment with moderate inhibitors of the CYP1A2 enzyme (propranolol, enoxacin).

Patients should be informed of a possible increase in suicidal thoughts and suicide, while careful supervision of these patients is necessary, especially at the beginning of treatment and when modifications in doses are made.

## Interactions[1]

Agomelatine is metabolized mainly through the CYP1A2 (90%) and CYP2C9 and CYP2C19 (10%) isoforms. Drugs that interact with these isoenzymes can reduce or increase the bioavailability of agomelatine. This drug should not be employed with potent inhibitors of the CYP1A2 isoenzyme (such as fluvoxamine and ciprofloxacin). Oestrogens (moderate inhibitors) produce increments in plasmatic levels of agomelatine and should therefore be administered with caution. Alcohol intake is not advised while the patient is under treatment.

## Special situations[1]

**Renal impairment:** use with precaution. **Liver impairment:** contraindicated. **Children and adolescents:** its use is not recommended as data is not available. **Pregnancy and breastfeeding:** No data is available on the use in pregnant women. Precaution is advised. Breast feeding should be stopped if agomelatine is indicated. **Elderly:** there is no demonstrated efficacy in patients > 65 years.

## Place in therapeutics

There is an ample amount of antidepressants available, and though their efficacy in treating depresión is similar, the profile of adverse effects among them differs. The ISRS are first line drugs employed in treating depression given their advantages over tricyclic agents in terms of feasibility in use and safety profiles.

There are no directly comparative studies between agomelatine and other antidepressants and its efficacy compared to placebo has doubtful clinical relevance. At 25 mg daily agomelatine seems inferior to the rest of antidepressants. With an increase to 50 mg daily it still remains unclear whether there is an improvement in efficacy. Experience with agomelatine is limited and greater liver toxicity has been observed especially with 50 mg daily doses.

For all these reasons, it is not clear what benefit agomelatine offers in relation to the incurred risk.

## Presentations

Valdoxan® (Servier). Agomelatine 25 mg 28 tablets (60.10 €). Requieres medical prescription.

## References

The complete report on agomelatine can be consulted at: http://www.navarra.es/medicamento

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