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EMA confirms positive benefit-risk for antidepressant Valdoxan/Thymanax (agomelatine)

Measures introduced to improve monitoring of liver function during treatment

The European Medicines Agency has completed a review of the anti-depressant medicine Valdoxan/Thymanax and concluded that its benefits continue to outweigh the risks. However, the Agency has recommended that further measures should be put in place to minimise the risk of liver toxicity. Valdoxan and Thymanax are two identical medicines used to treat major depression in adults.

A patient booklet will be distributed to all patients taking Valdoxan/Thymanax so that they are aware of the risk to the liver and the signs of liver problems to look out for. This booklet also includes information on the importance of monitoring liver function.

Warnings in the product information will also be strengthened to emphasise that liver function tests should be performed in patients both before starting the medicine and regularly during treatment. If tests suggest liver injury (i.e. increase of certain liver enzymes called transaminases in the blood to more than 3 times the upper limit of normal) doctors should not start their patients on Valdoxan/Thymanax or stop treatment of those who are already taking the medicine.

Valdoxan/Thymanax was first approved in 2009 on the basis of studies showing that the medicine has comparable effects to other antidepressants. Since the medicine has a different mode of action and a different safety profile to existing antidepressants, it was concluded that Valdoxan could be a valuable treatment for some patients as long as their liver function is tested regularly. However, side effects on the liver have continued to be reported and an observational study has shown a considerable level of non-compliance with the recommended liver monitoring programme. The Agency has therefore concluded that there is a need to reiterate the importance of liver monitoring, which is the cornerstone for the safe use of the product.

The new recommendations follow the most recent benefit-risk assessment of Valdoxan/Thymanax from the Agency's Pharmacovigilance Risk Assessment Committee (PRAC). As part of its recommendations, the PRAC had even considered that the use of Valdoxan/Thymanax should be contraindicated in patients aged 75 years or above since these patients might be at an increased risk of severe side effects on the liver and beneficial effects have not been documented in this population. The current product information for Valdoxan/Thymanax includes a warning that the medicine should not be used in patients aged 75 years or over. The CHMP considered that upgrading this warning to a contraindication in this population was not justified by the available data.

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The CHMP opinion will now be sent to the European Commission, which will issue a legally binding decision.

Information to patients

Liver problems have been reported in patients taking Valdoxan/Thymanax (agomelatine), used to treat major depression. To minimise the risk of liver damage, patients should be aware of the following:

- Before and regularly during treatment with Valdoxan/Thymanax, your doctor will check that your liver is working properly. If liver problems are detected, your doctor will stop your treatment immediately.
- It is important that you are aware of the signs and symptoms of liver injury, which include dark urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, and prolonged and unexplained tiredness. You should stop taking the medicine immediately and seek urgent medical advice if these symptoms appear.
- A patient booklet with more information on the risk of liver side effects will be distributed to all patients taking Valdoxan/Thymanax. If you have any questions or concerns you should speak to your doctor or pharmacist.

Information to healthcare professionals

Healthcare professionals should follow these recommendations:

- Baseline liver function tests should be performed in every patient and treatment should not be started in patients with transaminases exceeding 3 times the upper limit of normal.
- Liver function must be monitored regularly during treatment, at 3, 6, 12 and 24 weeks and regularly thereafter when clinically indicated.
- Treatment must be discontinued immediately if the increase in serum transaminases exceeds 3 times the upper limit of normal, or if patients present with symptoms or signs of potential liver injury.
- Patients should be informed of the symptoms of potential liver injury and the importance of liver function monitoring, and should be advised to stop taking Valdoxan/Thymanax immediately and to seek urgent medical advice if these symptoms appear.

More about the medicine

Valdoxan and Thymanax (agomelatine) are two identical medicines used to treat major depression in adults. Valdoxan/Thymanax was first authorised in the EU in February 2009. It is now marketed in all EU countries as well as Iceland.

The active substance in Valdoxan/Thymanax, agomelatine, is an antidepressant. It works in two ways, by stimulating the MT1 and MT2 receptors, which are normally activated by melatonin, and also by blocking the 5-HT_{2C} receptors, which are normally activated by the neurotransmitter 5-hydroxytryptamine (also called serotonin). This is thought to lead to increases in the levels of dopamine and noradrenaline between nerve cells in the areas of the brain that are involved in the

control of mood. This is believed to help relieve the symptoms of depression. Valdoxan/Thymanax might also help to normalise the patient's sleep patterns.

More about the procedure

The assessment of Valdoxan/Thymanax was a routine benefit-risk assessment, known as a periodic safety update report (PSUR) assessment. PSURs are periodic reports on the benefit-risk balance of a medicine submitted by companies at defined time points after a medicine's authorisation. During the assessment of PSURs, the Agency evaluates any new risks identified in order to determine whether the balance of benefits and risks of a medicine has changed and makes immediate proposals in relation to such risks.

The assessment was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's final opinion. The CHMP opinion will now be forwarded to the European Commission, which will issue a final decision in due course.

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