Important Safety Information

Prescribers Guide

Agomelatine

for the treatment of Major Depressive Episodes in Adults

Recommendations about:

- **Liver function monitoring**
- **Interaction with potent CYP1A2 inhibitors**

See the Summary of Product Characteristics

Agomelatine and risk of hepatotoxicity

Cases of liver injury*****, including hepatic failure (some of which had a fatal outcome or resulted in liver transplantation), elevations of liver enzymes exceeding 10 times upper limit of normal, hepatitis and jaundice have been reported in patients treated with Agomelatine. Most of them occurred during the first months of treatment. The pattern of liver damage is predominantly hepatocellular with a rise in serum transaminases which usually return to normal levels following cessation of Agomelatine. Patients with other hepatic risk factors appear to be more vulnerable.

*****Frequency: rare (≥1/10,000 to <1/1,000)

Recommendations for liver function monitoring

Do not use Agomelatine in cases of:

- **hepatic impairment (i.e. cirrhosis or active liver disease)**
- **or transaminases > 3 X ULN (Upper Limit of Normal)**

Before starting treatment:

Carefully evaluate risk factors for hepatic injury e.g

- obesity/overweight/non-alcoholic fatty liver disease
- diabetes
- alcohol use disorder and/or substantial alcohol intake
- concomitant medication associated with risk of hepatic injury

Perform baseline liver function tests in all patients before starting treatment:

- **do not start treatment in patients with baseline values of ALT and/or AST > 3 X ULN**
- exercise caution in patients with baseline values of ALT and/or AST > ULN and ≤ 3 X ULN

Perform transaminase tests (ALT/AST) in all patients

If the dose is increased, perform liver function tests at the same frequency as when initiating treatment. If a patient develops increased serum transaminases repeat his/her liver function tests within 48 hours.

*During treatment***:**

Discontinue Agomelatine treatment immediately if:

- the patient develops symptoms or signs of potential liver injury (such as **dark urine, light-coloured stools, yellow skin/eyes, right upper quadrant abdominal pain, sustained new-onset and unexplained fatigue**)
- the increase in **serum transaminases exceeds 3X ULN**

Following discontinuation of Agomelatine repeat liver function tests until serum transaminases return to normal.

Inform your patients about the importance of liver function monitoring and the symptoms of potential liver injury.

As part of discussions with your patients, please ensure that you give him/her a Patient Guide that he/she needs to read and keep during the course of their treatment. The Patient Guide will help your patients to understand the recommendations to avoid liver side effects and keep track of his/her blood test appointments.

Summary of recommendations for liver function monitoring

Finding	Action needed
ALT and/or AST increase ≤ 3 X ULN	Repeat the test within 48h
ALT and/or AST increase > 3 X ULN	Stop treatment immediately, repeat the blood tests until normalisation
Signs and symptoms of liver injury • dark urine • light coloured stools • yellow skin/eyes • right upper quadrant abdominal pain • sustained new-onset and unexplained fatigue	Stop treatment immediately, repeat the blood tests until normalisation

Interaction with potent CYP1A2 inhibitors

Agomelatine is contraindicated with concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine [Flaverin], ciprofloxacin [Ciproxin]).

Agomelatine is metabolised mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9/19 (10%). Medicines 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 an increase in agomelatine exposure.

In vivo, agomelatine does not induce CYP450 isoenzymes. Agomelatine inhibits neither CYP1A2 in vivo nor the other CYP450 in vitro. Therefore, Agomelatine is not expected to modify exposure to medicinal products metabolised by CYP450.