This document is approved by The Executive Directorate of Pharmacovigilance at SFDA

Valdoxan safety information

Good clinical care of liver function

Do not use Valdoxan® in case of:

- **Hepatic impairment (**ie, cirrhosis or active liver disease).
- **In patients with transaminases exceeding 3 times the upper limit of normal (ULN).**
- **Concomitant use of potent CYP1A2 inhibitors (**eg, fluvoxamine, ciprofloxacin**).**

Before starting the treatment:

- **Risk factors for hepatic injury should be carefully evaluated, eg, obesity/overweight/nonalcoholic fatty liver disease, diabetes, alcohol use disorder and/or substantial alcohol intake, concomitant medicines associated with risk of hepatic injury.**
- **Baseline liver function tests should be performed in every patient.**
- **Caution should be exercised in patients with ALT/AST >1 ULN and ≤3 ULN.**

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.

Prescribe transaminase tests (ALT/AST) to your patients:

	Before initiation or dose increase	Around week 3	Around week 6	Around week 12	Around week 24
Blood tests	✓	✓	✓	✓	✓

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What to do in the case of:

ALT/AST increase ≤3 ULN	→	**Repeat the test within 48 h**
ALT/AST increase >3 ULN	→	**Stop the treatment immediately, repeat the blood tests until normalization**
Signs and symptoms of liver injury*	→	**Stop the treatment immediately, repeat the blood tests until normalization**

**Dark urine, light-colored stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue.*

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.