

PHYSICIAN'S GUIDE

Agomelatine Rowex 25 mg Film-coated tablets

agomelatine

In the treatment of Major Depressive Episodes in Adults

INFORMATION FOR HEALTHCARE PROFESSIONALS

Recommendations regarding

- Liver function monitoring
- Interaction with potent CYP1A2 inhibitors

Agomelatine and risk of hepatotoxicity

- Cases of liver injury, including hepatic failure (few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors), elevations of liver enzymes exceeding 10 times upper limit of normal, hepatitis and jaundice have been reported in patients treated with Agomelatine in the post-marketing setting. Most of them occurred during the first months of treatment. The pattern of liver damage is predominantly hepatocellular with serum transaminases which usually return to normal levels on cessation of Agomelatine.

Recommendations for liver function monitoring

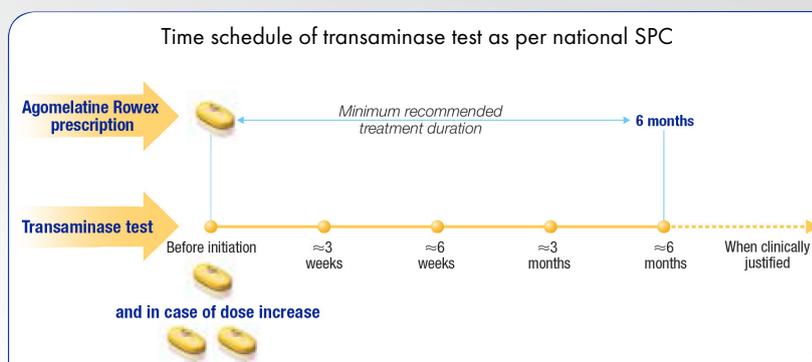
- *Do not use Agomelatine in case of*
Hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases > 3ULN
- *Before starting treatment*
Caution for Agomelatine initiation in patients with hepatic injury risk factors

Agomelatine should be prescribed after careful consideration of benefit and risk:
 in patients with hepatic injury risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, alcohol use disorder and /or substantial alcohol intake
 in patients receiving concomitant medicinal products associated with risk of hepatic injury.

Checking patient's liver function tests

Baseline liver function tests should be undertaken in all patients before starting treatment:

- treatment should not be initiated in patients with baseline values of ALT and/or AST > 3 ULN.
- caution should be exercised in patients with baseline values of ALT and/or AST > ULN and ≤ 3 ULN.
- Prescribe transaminases tests (ALT/AST) for your patients



When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment. Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours.

Please see the Liver Monitoring Scheme with Agomelatine on the next page to assist you with this.

• During treatment period

Agomelatine treatment should be discontinued immediately if:

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

Following discontinuation of Agomelatine therapy liver function tests should be repeated until serum transaminases return to normal.

Inform your patient about:

- the importance of liver function monitoring and,
- the vigilance about signs and symptoms of liver injury.

Reminder:

What to do in case of:

ALT and /or AST increase ≤ 3 ULN	Repeat the test within 48h
ALT and/or 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

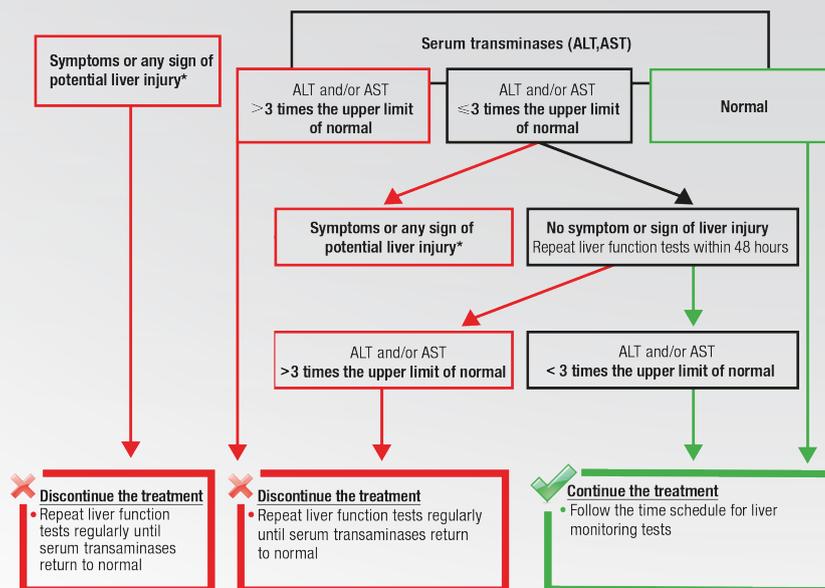
* dark urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue

Liver function monitoring scheme with Agomelatine

Patient name:.....

Date of initiation:.....

<input type="checkbox"/> Agomelatine 25 mg		<input type="checkbox"/> In case of dose increase at 50mg, restart the monitoring scheme.	
<input type="checkbox"/> Before Initiation of 25mg	ALT.....U/L	<input type="checkbox"/> Initiation of 50mg	ALT.....U/L
	AST.....U/L		AST.....U/L
<input type="checkbox"/> Week 3	ALT.....U/L	<input type="checkbox"/> Week 3	ALT.....U/L
	AST.....U/L		AST.....U/L
<input type="checkbox"/> Week 6	ALT.....U/L	<input type="checkbox"/> Week 6	ALT.....U/L
	AST.....U/L		AST.....U/L
<input type="checkbox"/> Week 12	ALT.....U/L	<input type="checkbox"/> Week 12	ALT.....U/L
	AST.....U/L		AST.....U/L
<input type="checkbox"/> Week 24	ALT.....U/L	<input type="checkbox"/> Week 24	ALT.....U/L
	AST.....U/L		AST.....U/L
Please perform a test at any time if clinically justified.		Please perform a test at any time if clinically justified.	



*Such as dark urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue.

Interaction with potent CYP1A2 inhibitor

- Agomelatine is contraindicated with concomitant use of potent CYP1A2 inhibitors [e.g. fluvoxamine [Faverin®], ciprofloxacin [Ciproxin®]].
- Agomelatine is metabolized 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 metabolized by CYP450.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk of the medicinal product. Patients are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +3531 6764971; Fax: +3531 6762517. Website: www.hpra.ie; Adverse events should also be reported to Rowex Ltd. by emailing pv@rowa-pharma.ie or phone: tel: +353 27 50077 or fax: +353 27 50417