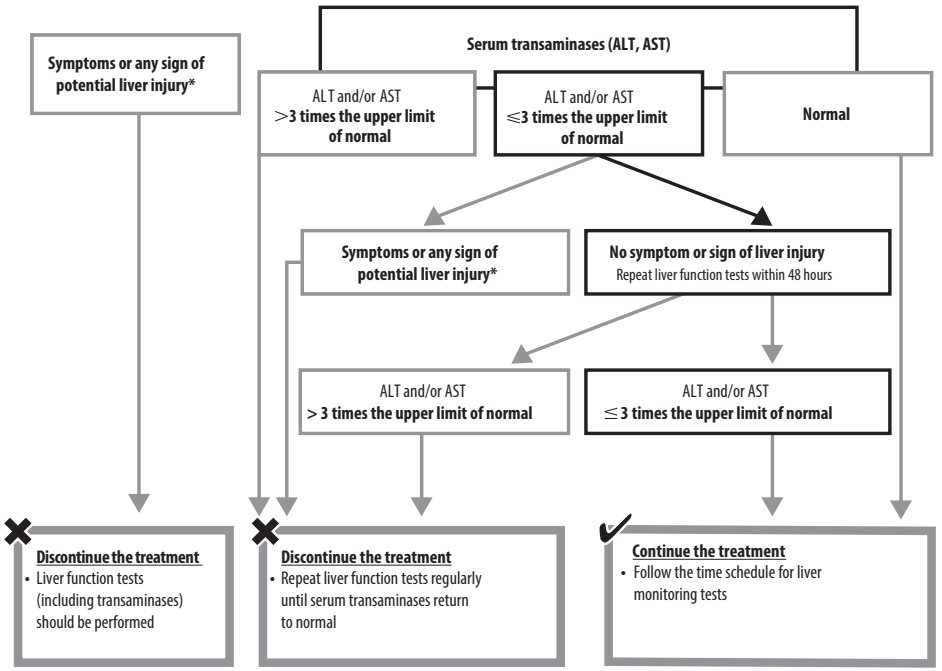
## Liver Monitoring Scheme with Agomelatine

**Patient Name:** _____ **Date of initiation:** _____

| Agomelatine 25 mg Film-coated Tablets | | Dose increase to 50 mg – restart monitoring scheme | |
|---|---|---|---|
| ☐ Before initiation | ALT_____U/L<br>AST U/L | ☐ Before initiation | ALT_____U/L<br>AST U/L |
| ☐ Week 3 | ALT_____U/L<br>AST U/L | ☐ Week 3 | ALT_____U/L<br>AST U/L |
| ☐ Week 6 | ALT_____U/L<br>AST U/L | ☐ Week 6 | ALT_____U/L<br>AST U/L |
| ☐ Week 12 | ALT_____U/L<br>AST U/L | ☐ Week 12 | ALT_____U/L<br>AST U/L |
| ☐ Week 24 | ALT_____U/L<br>AST U/L | ☐ Week 24 | ALT_____U/L<br>AST U/L |

Please perform a test at any time if clinically justified.




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

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## PHYSICIAN'S GUIDE

IMPORTANT INFORMATION - DO NOT DISCARD!

# Agomelatine 25 mg Film-Coated Tablets

**In the treatment of Major Depressive Episodes in Adults**

# INFORMATION FOR HEALTHCARE PROFESSIONALS

This is risk minimisation material and is provided as a collaborative project between Accord Healthcare Ireland Ltd. and (Mylan) McDermott Laboratories Ltd t/a Gerard Laboratories. For further information, please refer to the Summary of Product Characteristics (SmPC) for the respective medicinal products from the relevant Marketing Authorisation Holder available at www.hpra.ie.

### 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 cases occurred during the first months of treatment. The pattern of liver damage is predominantly hepatocellular with elevated serum transaminases which usually return to normal levels following cessation of Agomelatine.

**Detailed information can be found in the Summary of Product Characteristics (SPC).**

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

## Recommendations for liver function monitoring

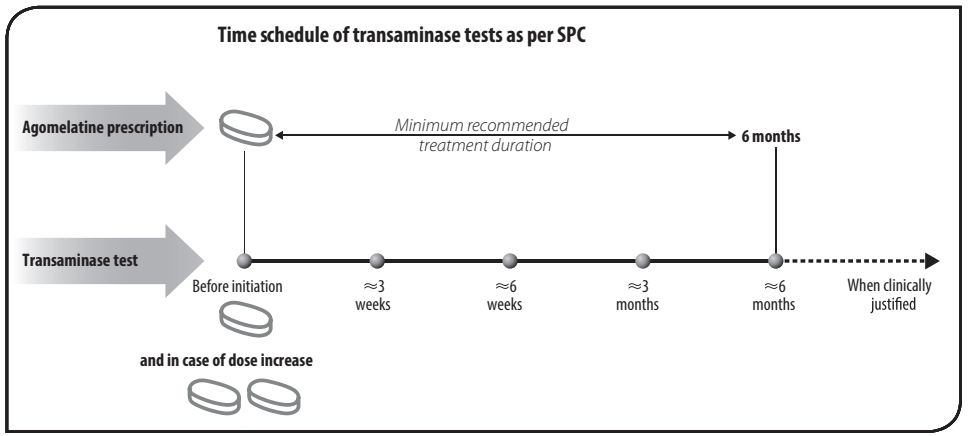
Do not use Agomelatine in case of:

- Hepatic impairment (i.e. cirrhosis or active liver disease)
- Or transaminases > 3 x ULN (upper limit of normal)

Before starting treatment

Agomelatine should be prescribed after careful consideration of benefit and risk:

- **Carefully evaluate risk factors for hepatic injury for example:**
  - obesity/overweight/non-alcoholic fatty liver disease
  - diabetes
  - alcohol use disorder and /or substantial alcohol intake
  - concomitant medicinal products associated with risk of hepatic injury.
- **Perform baseline liver function tests in all patients before starting treatment:**
  - treatment should not be initiated in patients with baseline values of ALT and/or AST > 3 x ULN.
  - caution should be exercised in patients with baseline values of ALT and/or AST > ULN and ≤ 3 x ULN.
- **Perform transaminases tests (ALT/AST) in all 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 **Liver Monitoring Scheme with Agomelatine** at the back of this guide 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, right upper quadrant abdominal pain, sustained new-onset and unexplained fatigue),
- the increase in serum transaminases exceeds 3 x 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,
- signs and symptoms of potential liver injury.

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

**Reminder- What to do in case of:**

| | | |
|---|---|---|
| ALT and/or AST increase ≤ 3 x ULN | ⇨ | Repeat the blood test within 48 hours |
| ALT and/or AST increase > 3 x ULN | ⇨ | Stop treatment immediately and repeat the blood tests until normalisation. |
| Signs and symptoms of liver injury * | ⇨ | Stop treatment immediately and repeat the blood tests until normalisation. |

*dark urine, light coloured stools, yellow skin/eyes, right upper quadrant abdominal pain, 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 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.

## Reporting Adverse Events

Suspected adverse reactions should be reported to the Health Products Regulatory Authority via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.
Adverse reactions can also be reported to Accord Healthcare Ireland Ltd. via E-mail: medinfo@accord-healthcare.com; Tel: +44 (0) 1271 385 257; or by completing the online form at www.accord-healthcare.ie/drug-reaction-report or to McDermott Laboratories Ltd t/a Gerard Laboratories, Email: ukpharmacovigilance@mylan.com Tel:+44 174 882 8888.

## Further information

Additional electronic copies of this material are available at www.hpra.ie.
Additional hard copies of this material can be requested by contacting the relevant Marketing Authorisation Holder at the following contact points:
Accord Healthcare Ireland Limited, Euro House, Euro Business Park, Little Island Cork, T45 K857, Ireland. via Email:medinfo@accord-healthcare.com Tel:+44 1271 385257 or to McDermott Laboratories Ltd t/a Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland. Tel:+353 1 8322250.