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Agomelatine Lupin
Prescriber Guide

IMPORTANT INFORMATION – DO NOT DISCARD!

Agomelatine Lupin is used in the treatment of major depressive episodes in adults.

This Prescriber Guide provides information for Healthcare Professionals with recommendations regarding:

- liver function monitoring; and
- interaction with potent CYP1A2 inhibitors.

Please refer to the Product Information for additional information.

Agomelatine Overview

Agomelatine was registered in Australia in August 2010 and has been available since 2010 for the treatment of major depression in adults including prevention of relapse.

Agomelatine and Risk of Hepatotoxicity

The following have been reported in patients treated with Agomelatine post-marketing:

- cases of liver injury[1], including hepatic failure (some of which had a fatal outcome or resulted in liver transplantation);
- elevations of liver enzymes exceeding 10 times the upper limit of normal;
- hepatitis; and
- jaundice.

Most of these occurred during the first months of treatment. The pattern of liver damage is predominantly hepatocellular with serum transaminases usually returning to normal levels following discontinuation of agomelatine.

Some patients may have hepatic risk factors and appear to be more vulnerable. This highlights the importance of performing liver function tests in all patients.

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

Recommendations for Liver Function Monitoring

Do not use Agomelatine Lupin in cases of:

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

Before Starting Treatment

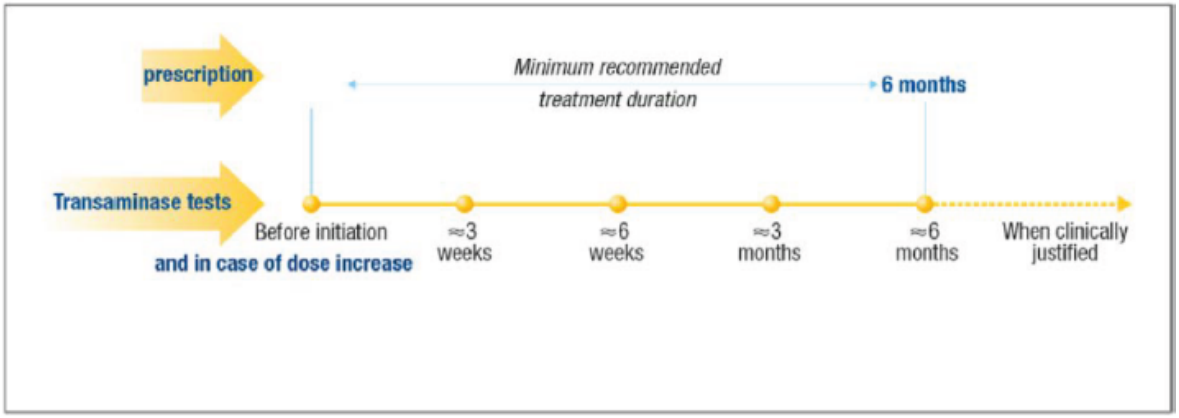
Carefully evaluate risk factors for hepatic injury, eg:

- 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 every patient before starting treatment. Note:

- Do no initiate 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 (ALTIAS1) in all patients, as per below figure.



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 their liver function tests within 48 hours.

During Treatment

Discontinue Agomelatine Lupin 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 3 X ULN.**

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

Inform your patients about:

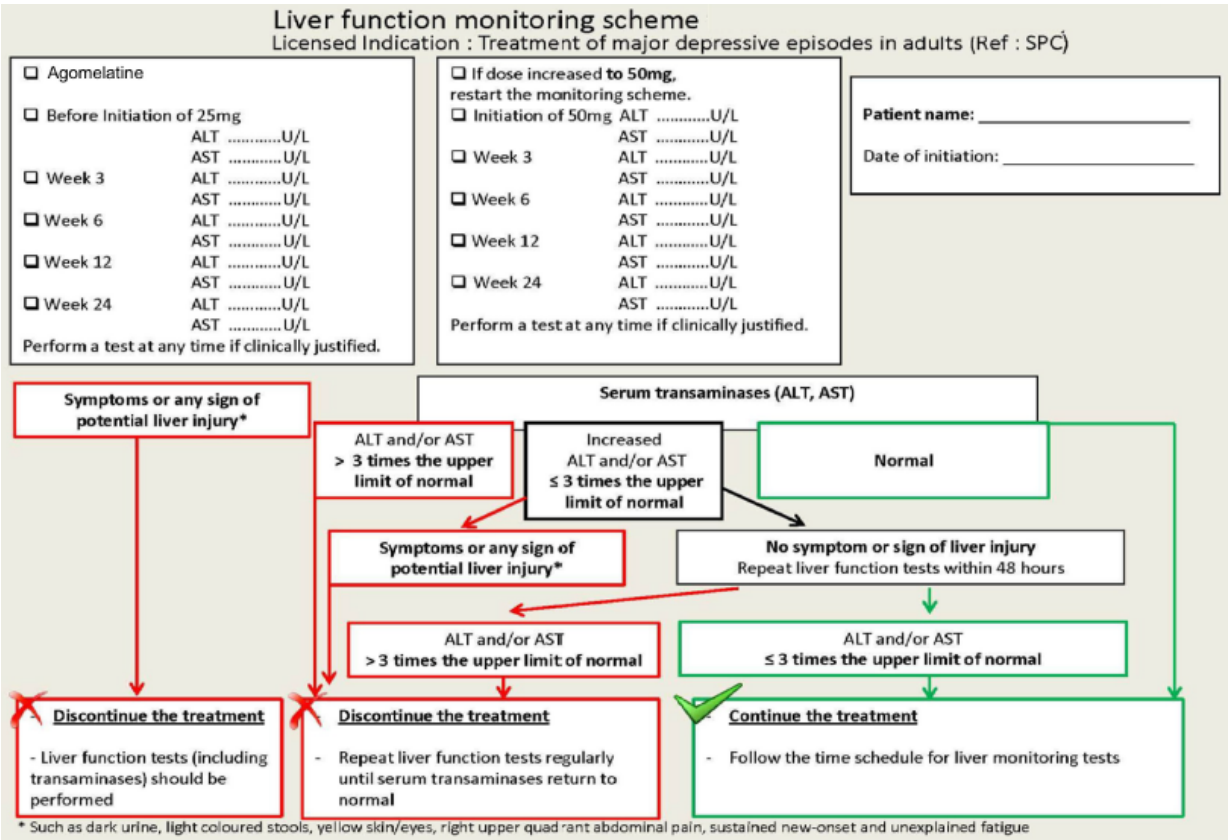
- the importance of liver function monitoring; and
- the symptoms of potential liver injury.

As part of discussions with your patients, please ensure that you print them a Consumer Medicine Information leaflet that they need to read and keep during the course of their treatment (available on our company website [www.generichealth.com.au/Product Listing] or the TGA website [www.ebs.tga.gov.au/Agomelatine Lupin CMI]). The Consumer Medicine Information leaflet will help your patients to understand the recommendations to avoid liver side effects and keep track of their blood test appointments.

Refer to Table 1 for a summary of recommendations for liver function monitoring.

Table 1: Summary of Recommendations for Liver Function Monitoring

Finding	Action Needed
ALT and/or AST increase ≤3 X ULN.	Repeat the test within 48 hours.
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; • 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 Lupin is contraindicated with concomitant use of potent CYP1A2 inhibitors (eg. fluvoxamine, ciprofloxacin).

Agomelatine is metabolised mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9/19 (10%). Medicines that interact with these isoenzymes may decease 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 Lupin is not expected to modify exposure to medicinal products metabolised by CYP450.

Further Information

For further information, or to request further copies of this guide, please contact the Generic Health Medical Information Team on:
Phone: **03 9809 7900**
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