PLEASE READ

IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA

An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Ontozry▼ (cenobamate): new requirements for liver monitoring due to reports of severe liver injury

12th May, 2026,

Dear Healthcare Professional,

Angelini Pharma UKI Limited in agreement with the European Medicines Agency and the Health Products Regulatory Authority would like to inform you of the following:

Summary

- **Cases of severe liver injury with hepatic failure have been reported in patients treated with Ontozry, many in the context of polytherapy with other antiseizure medications.**
- **Liver function tests should be evaluated before initiation of Ontozry and liver function should be monitored during treatment.**
- **Prompt clinical evaluation and liver function tests should be performed in patients presenting with signs or symptoms indicating liver injury.**
- **Patients should be advised to immediately seek medical attention if they experience signs or symptoms suggesting liver injury.**
- **If liver injury is suspected or detected, dose reduction or discontinuation of Ontozry should be considered.**

Background on the safety concern

Ontozry is an antiepileptic medication indicated in the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 antiepileptic medicinal products.

Elevated hepatic enzymes are commonly observed with Ontozry treatment; pooled double-blind clinical studies reported alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases in 1.6% and 1.4% of Ontozry-exposed patients, respectively, compared to 0% and 0.4% in the placebo group. A dose-dependent trend was evident, with elevations reaching 3.6% for ALT and 2.7% for AST among those receiving the maximum daily dose of Ontozry (i.e. 400 mg). An evaluation of this particular safety issue identified 4 cases of severe liver injury likely associated with Ontozry, including one case that fulfilled the criteria for Hy's Law (a method to predict a drug's likelihood to induce severe liver injury). Additionally, 24 cases, which were considered to be possibly related to Ontozry, were also documented.

Most reports of severe liver injuries potentially associated with Ontozry have arisen when it is used alongside other antiseizure medications. The causes and mechanisms of Ontozry-related liver toxicity remain mostly unclear.

Given the newly recognised risk of severe liver injury, serum transaminases (ALT and AST), gamma-glutamyl transferase (GGT), alkaline phosphatase and total bilirubin should be checked prior to initiating Ontozry therapy and monitored during treatment. Clinical evaluation and liver function testing should be conducted promptly in patients presenting with signs or symptoms indicative of hepatic injury, such as fatigue, anorexia, right upper quadrant abdominal pain, dark urine, or jaundice. Patients should also be advised to recognise signs or symptoms suggestive of liver injury and to seek medical attention without delay if they occur.

If liver injury is suspected or detected, dose reduction or discontinuation of Ontozry should be considered according to the guidelines in the summary of product characteristics (i.e. avoid abrupt discontinuation unless required, to minimize the risk of rebound seizures).

The product information of Ontozry will be updated in line with this new safety information. This includes revised warnings reflecting the recommendations above. Furthermore, liver injury is added as a rare side effect (which may occur in up to 1 in 1,000 people) in Ontozry's product information.

Call for reporting

▼ Ontozry is subject to additional monitoring, meaning that it is monitored even more intensively than other medicines.

Healthcare professionals should report any adverse events suspected to be associated with the use of Ontozry via HPRA Pharmacovigilance, website: www.hpra.ie.

Adverse events and product complaints should also be reported to Angelini Pharma on +353 1 584 4671 or UKIReporting@angelinipharma.com

Company contact point

For further information please email UKIMedical@angelinipharma.com, or call +353 1 584 4671, or write to: Angelini Pharma UK & Ireland, 6th floor, Napier House, 24 High Holborn, WC1V 6AZ London, United Kingdom

Yours sincerely,

DocuSigned by:
Ahmed Eltayb
144A8A7EBAE5420...

Dr Ahmed H Eltayb
Medical Director

Angelini Pharma UK & Ireland
6th floor, Napier House, 24 High Holborn, WC1V 6AZ London, United Kingdom