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

Dear Healthcare Professional,

Angelini Pharma S.p.A. [or local Affiliate Name] in agreement with the European Medicines Agency and the [National Competent 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 a 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 anti-epileptic medicinal products.

Elevated hepatic enzymes are commonly observed with Ontozry treatment; pooled double-blind clinical studies reported ALT and 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 anti-seizure 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 cenobamate 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 the Ontozry's product information.

Call for reporting

Healthcare professionals should report any adverse events suspected to be associated with the use of Ontozry according to national reporting requirements.

[Affiliate to please include name, postal address, fax number, website address of the national spontaneous reporting system]

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

Company contact point

[Affiliate to please include contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address]

Yours sincerely,

[Company Name of Affiliate]

[Signature of authorised contact person]

Communication Plan for Ontozry DHPC in the EU

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	ONTOZRY (cenobamate)
Marketing authorisation holder(s)	Angelini Pharma S.p.A. [or local Affiliate Name]
Safety concern and purpose of the communication	Updated recommendations to prevent the risk of severe liver injury
DHPC recipients	Neurologists, general practitioners, specialists in hepatology and gastroenterology, professional societies in neurology and in hepatology/ gastroenterology, hospital and community pharmacist. The target group should be further defined at national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	To be defined by PRAC (all EU-Member States or DHPC distribution left to national decision)

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	10 April 2026
DHPC and communication plan (in English) agreed by CHMP	23 April 2026
Submission of translated DHPCs to the national competent authorities for review	28 April 2026
Agreement of translations by national competent authorities	05 May 2026
Dissemination of DHPC	12 May 2026