<Date>

Direct Healthcare Professional Communication (DHPC)

Mavenclad (cladribine) – risk of serious liver injury and new recommendations about liver function monitoring

Dear Healthcare Professional,

Merck Healthcare KGaA in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you about adverse events of liver injury under the treatment with Mavenclad:

Summary

- Liver injury, including serious cases, has been reported in patients treated with Mavenclad.
- Before initiating treatment, a detailed patient history of underlying liver disorders or episodes of liver injury with other medicines should be undertaken.
- Liver function tests including serum aminotransferase, alkaline phosphatase, and total bilirubin levels should be assessed prior to initiation of therapy in year 1 and year 2.
- During treatment, liver function tests should be conducted, and repeated as necessary. In case a patient develops liver injury, treatment with Mavenclad should be interrupted or discontinued, as appropriate.

Background on the safety topic

Mavenclad (cladribine) is indicated for the treatment of adult patients with highly active relapsing multiple sclerosis (MS).

Liver injury, including serious cases and cases leading to discontinuation of treatment, has been reported in patients treated with Mavenclad. A recent review of available safety data has concluded on an increased risk for liver injury following treatment with Mavenclad.

Most cases of liver injury concerned patients with mild clinical symptoms. However, in rare cases, a transient transaminase elevation exceeding 1000 units per litre and jaundice was described. Time to onset varied, with most cases occurring within 8 weeks after the first treatment course.

The review of liver injury cases did not identify a clear mechanism. Some patients had a history of previous episodes of liver injury with other medicines or had underlying liver disorders. Data from clinical trials did not suggest a dose dependent effect.

Liver injury has been included in the product information of Mavenclad as an adverse drug reaction of uncommon frequency. In addition, the product information has been updated with new warnings and precautions regarding liver injury, including recommendations to obtain patient history for underlying liver disorders or previous liver injury, and to assess liver function tests prior to treatment initiation in year 1 and 2. The prescribers' guide and the patient guide of Mavenclad will be updated to include information about liver adverse events.
Patients should be advised to report immediately to their healthcare professional any signs or symptoms of liver injury.

Call for reporting

Reporting suspected adverse reactions after authorization of the medicinal product is important to ensure patient safety. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
<details on the national reporting system>

Company contact point
<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Mavenclad (Cladribine) 10 mg tablets
Marketing authorisation holder(s)	Merck Europe B.V.
Safety concern and purpose of the communication	Risk of serious liver injury in MS patients treated with Mavenclad. The DHPC intends to inform prescribers about occurrence of cases of liver injury in patients treated with Mavenclad, and on the actions to be taken before and during treatment.
DHPC recipients	Neurologists, general practitioners, specialists in Hepatology and Gastroenterology, MS treatment clinics, professional societies in neurology and in hepatology/gastroenterology, and other recipients to be agreed with the National Competent Authorities (NCAs). Details for each country to be discussed and agreed with the National Competent Authorities (NCAs).
Member States where the DHPC will be distributed	The communication will be disseminated in all European Economic Area (EEA) countries where Mavenclad is marketed.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	13 January 2022
DHPC and communication plan (in English) agreed by CHMP	17 January 2022
Submission of translated DHPCs to the national competent authorities for review	24 January 2022
Agreement of translations by national competent authorities	31 January 2022
Dissemination of DHPC	14 February 2022