<Date>

Tecfidera® (dimethyl fumarate): Updated recommendations in the light of cases of progressive multifocal leukoencephalopathy (PML) in the setting of mild lymphopenia

Dear Healthcare Professional,

In agreement with the European Medicines Agency (EMA) and the [National Competent Authority] Biogen Netherlands B.V. would like to inform you of important updated information to help minimise the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with Tecfidera.

Summary

- **Cases of progressive multifocal leukoencephalopathy (PML) in the setting of mild lymphopenia (lymphocyte count ≥ 0.8 $\times 10^9$/L and below the lower limit of normal) have been reported in patients treated with Tecfidera; previously, PML had been confirmed only in the setting of moderate to severe lymphopenia.**

- **Tecfidera is contraindicated in patients with suspected or confirmed PML.**

- **Tecfidera should not be initiated in patients with severe lymphopenia (lymphocyte counts < 0.5 $\times 10^9$/L).**

- **If the lymphocyte count is below the normal range, a thorough assessment of possible causes should be completed before initiating treatment with Tecfidera.**

- **Tecfidera should be discontinued in patients with severe lymphopenia (lymphocyte counts < 0.5 $\times 10^9$/L) persisting for more than 6 months.**

- **If a patient develops PML, Tecfidera must be permanently discontinued.**

- **Advise patients to inform their partner or caregivers about their treatment and symptoms suggestive of PML, since they may notice symptoms of which the patient is not aware.**

Background on the safety concern

Tecfidera is authorised in the European Union for the treatment of adults with relapsing-remitting multiple sclerosis. Tecfidera may cause lymphopenia: in clinical trials lymphocyte counts decreased by approximately 30% of baseline value during treatment.

PML is a serious opportunistic infection caused by the John-Cunningham virus (JCV), which may be fatal or result in severe disability. Risk factors for developing PML in the presence of JCV include an altered or weakened immune system.

Among over 475,000 patients exposed to Tecfidera, 11 cases of PML have been confirmed. The single commonality in all 11 confirmed cases is a decreased absolute lymphocyte count (ALC), which is a biologically plausible risk factor for PML. Three of these cases occurred in the setting of mild lymphopenia, while the remaining eight cases developed during moderate to severe lymphopenia.

As currently recommended, all patients should have absolute lymphocyte counts (ALC) measured before initiating treatment and every 3 months thereafter.

In patients with lymphocyte counts below the lower limit of normal as defined by local laboratory reference range, enhanced vigilance is now recommended and additional factors that may potentially contribute to an increased risk for PML in patients with lymphopenia should be considered. These include:

- duration of Tecfidera therapy. Cases of PML have occurred after approximately 1 to 5 years of treatment, although the exact relationship with duration of treatment is unknown;
- profound decreases in CD4+ and especially in CD8+ T cell counts;
- prior immunosuppressive or immunomodulatory therapy;

In patients with sustained moderate reductions of absolute lymphocyte counts $\geq 0.5 \times 10^9$/L and $<0.8 \times 10^9$/L for more than six months, the benefit/risk of Tecfidera treatment should be re-assessed.

In addition,

- physicians should evaluate their patients to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are typical of MS or possibly suggestive of PML;
- at the first sign or symptom suggestive of PML, Tecfidera should be withheld and appropriate diagnostic evaluations carried out, including determination of JCV DNA in cerebrospinal fluid (CSF) by quantitative polymerase chain reaction (PCR) methodology;
- it is important to note that patients developing PML following recent discontinuation of natalizumab may not present with lymphopenia.

The Tecfidera Product Information is being revised to include the above information.

Call for reporting
Healthcare professionals should report any suspected adverse reactions associated with the use of Tecfidera in accordance with the national requirements via the national spontaneous reporting system, to:
<Details of national reporting systems as per Appendix V to be included prior to submission to national MS competent Authorities>

Company contact point
Contact point details for further information to be completed locally.

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNCIATION PLAN	
Medicinal product/active substance	Tecfidera® (dimethyl fumarate)
Marketing authorisation holder	Biogen Netherlands B.V.
Safety concern and purpose of the communication	Updated recommendations in the light of cases of progressive multifocal leukoencephalopathy (PML) in the setting of mild lymphopenia
DHPC recipients	Healthcare Providers treating multiple sclerosis (MS), consultant neurologists and MS specialist nurses and other recipients to be agreed with the National Competent Authorities (NCAs).
Member States where the DHPC will be distributed	In all countries where the product is launched.

Timetable	
Action	**Date**
DHPC and communication plan (in English) agreed by PRAC	1 October 2020
DHPC and communication plan (in English) agreed by CHMP	15 October 2020
Submission of translated DHPCs to the national competent authorities for review	22 October 2020
Agreement of translations by national competent authorities	29 October 2020
Dissemination of DHPC	12 November 2020