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This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA

# Direct Healthcare Professional Communication

## Defra 120® mg and Defra 240® mg (Dimethyl fumarate): Updated recommendations in the light of cases of progressive multifocal leukoencephalopathy (PML) in the setting of mild lymphopenia.

**Dear Healthcare professional,**

MS Pharma Saudi in agreement with the Saudi Food and Drug Authority (SFDA), would like to inform you of important updated information to help minimise the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with dimethyl fumarate.

**Summary**

- Cases of progressive multifocal leukoencephalopathy (PML) in the setting of **mild** lymphopenia (lymphocyte count ≥ 0.8 ×109/L and below the lower limit of normal) have been reported in patients treated with Dimethyl fumarate; previously, PML had been confirmed only in the setting of moderate to severe lymphopenia.
- Dimethyl fumarate is contraindicated in patients with suspected or confirmed PML.
- Dimethyl fumarate should not be initiated in patients with severe lymphopenia (lymphocyte counts < 0.5 ×109/L).
- If the lymphocyte count is below the normal range, a thorough assessment of possible causes should be completed before initiating treatment with Dimethyl fumarate.
- Dimethyl fumarate should be discontinued in patients with severe lymphopenia (lymphocyte counts < 0.5 ×109/L) persisting for more than 6 months.
- If a patient develops PML, Dimethyl fumarate 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:

Defra® 120mg and Defra® 240mg is authorised in Saudi Arabia for the treatment of adults with relapsing remitting multiple sclerosis. Dimethyl fumarate 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 Dimethyl fumarate, 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 Dimethyl fumarate 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 ≥0.5 x 109/L and <0.8x109/L for more than six months, the benefit/risk of Dimethyl fumarate 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, Dimethyl fumarate 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.

**Call for reporting for adverse reactions**
**The National Pharmacovigilance and Drug Safety Centre (NPC):**

- Website: http://ade.sfda.gov.sa/
- E-mail: npc.drug@sfda.gov.sa
- Call center number: 19999

**Company contact point**
**Pharmacovigilance department in (MS Pharma Saudi)**

- Telephone: 00966112790122 Exten: 6013
- Mobile: 00966548933555
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