Date: 25th November 2015

Subject: Tecfidera® (dimethyl fumarate)**: new measures to minimise the risk of PML –enhanced monitoring and stopping rules**

Dear Healthcare Professional

In agreement with the European Medicines Agency (EMA) and the Health Products Regulatory Agency (HPRA) Biogen would like to inform you of important new measures to minimise the risk of progressive multifocal leukoencephalopathy (PML) with Tecfidera.

Summary

We recommend that the following actions are taken to reduce the risk of PML:

- Before starting treatment with Tecfidera:
  - ensure a complete blood count (including lymphocytes) is performed
  - a baseline reference MRI should be available (usually within 3 months)
  - counsel patients and carers on the risk of PML, the possible clinical symptoms to be aware of and actions to take if any of these symptoms arise

- After starting treatment with Tecfidera:
  - monitor complete blood counts including lymphocytes every 3 months
  - because of a possible increased risk of PML, consider interrupting Tecfidera in patients with lymphocyte counts below $0.5x10^9$/L persisting for more than 6 months (i.e. severe prolonged lymphopenia)
  - if treatment is stopped due to lymphopenia, monitor patients until lymphocyte levels return to normal

- Other considerations:
  Note that PML can only occur in the presence of a John-Cunningham virus (JCV) infection. If JCV testing is undertaken, it should be considered that the influence of lymphopenia on the accuracy of anti-JCV antibody test has not been studied in patients treated with Tecfidera. It should also be noted that a negative anti- JCV antibody test (in the presence of normal lymphocyte counts) does not preclude the possibility of subsequent JCV infection.

- If treatment is continued in patients with severe prolonged lymphopenia, enhanced vigilance for PML is recommended:
  - counsel patients and carers again regarding the risk of PML in the presence of risk factors and remind them of the early clinical symptoms to be aware of
  - monitor patients for signs and symptoms or appearance of new neurological dysfunction (e.g. motor dysfunction, cognitive or psychiatric

symptoms). Consider that PML can present with similar features to those of multiple sclerosis because both are demyelinating diseases
  - consider the need for further MRI imaging as part of increased vigilance for PML, in accordance with national and local recommendations.

- In any patient, if PML is suspected, stop treatment with Tecfidera immediately and investigate appropriately.

Further information on the safety concern

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

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

In October 2014, a fatal case of PML was reported in a patient from a long-term extension study who was treated with dimethyl fumarate for 4.5 years. The patient experienced severe prolonged lymphopenia (>3.5 years) while on Tecfidera. This confirmed case of PML was the first reported for Tecfidera. Two other post-marketing confirmed cases have been reported from USA and Germany in 2015 so far*, both in male patients (aged 64 and 59 years respectively) taking Tecfidera for 2 and approximately 1.5 years in total, respectively. PML diagnoses occurred after <1.5 years and approximately 1 year after the onset of severe prolonged lymphopenia (lymphocyte counts $\leq 0.5 \times 10^9$/L with nadir of 0.3×10^9/L and mainly $<0.5 \times 10^9$/L, respectively). None of the three patients had previously received medicines known to be associated with a risk of PML. All patients were seropositive for anti-JCV antibodies at the time of PML diagnosis.
*(confirmed by 30 October 2015)

Call for reporting

Healthcare professionals should report any suspect adverse reactions associated with the use of Tecfidera in accordance with the national requirements via the national spontaneous reporting system, to: HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 676 4971; Fax: +353 1 676 2517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

ADRs can also be reported to the Marketing Authorisation Holder (MAH) by telephone (1800 812 719), fax [+44 (0) 1748 828801] or email (biogen@professionalinformation.co.uk).

Company contact point
Contact point details for further information are given in the product information of the medicinal product (SmPC and PIL) at http://www.ema.europa.eu/ema/.

Yours faithfully

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ANNEX I

Revised Labelling (changes underlined in bold)

From SmPC

4.4 Special warnings and precautions for use

Changes in renal and hepatic laboratory tests have been seen in clinical trials in subjects treated with Tecfidera (see section 4.8). The clinical implications of these changes are unknown. Assessments of renal function (e.g. creatinine, blood urea nitrogen and urinalysis) and hepatic function (e.g. ALT and AST) are recommended prior to treatment initiation, after 3 and 6 months of treatment, every 6 to 12 months thereafter and as clinically indicated.

Patients treated with Tecfidera may develop severe prolonged lymphopaenia (see section 4.8). Tecfidera has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients. Prior to initiating treatment with Tecfidera, a **current** complete blood count, **including lymphocytes, must** be performed. **If lymphocyte count is found to be below the normal range, thorough assessment of possible causes should be completed prior to initiation of treatment with Tecfidera.**

After starting therapy, complete blood counts**, including lymphocytes, must be performed every 3 months. Consider interruption of Tecfidera in patients with lymphocyte counts <0.5x10^9/L persisting for more than 6 months. The benefit/risk balance of the therapy should be reconsidered in discussion with the patient in the context of other therapeutic options available. Clinical factors, evaluation of any laboratory and imaging investigations could be included as part of this re-consideration. If treatment is continued despite a persistent lymphocyte count < 0.5x10^9/L, enhanced vigilance is recommended (see also subsection on PML).**

Lymphocyte counts should be followed until recovery. Upon recovery and in the absence of alternative treatment options, decisions about whether or not to restart Tecfidera after treatment discontinuation should be based on clinical judgement.

MR imaging

Before initiating treatment with Tecfidera, a baseline MRI should be available (usually within 3 months) as a reference. The need for further MRI scanning should be considered in accordance with national and local recommendations. MRI imaging may be considered as part of increased vigilance in patients considered at increased risk of PML. In case of clinical suspicion of PML, MRI should be performed immediately for diagnostic purposes.

Progressive Multifocal Leukoencephalopathy (PML)

PML cases have occurred with Tecfidera and other products containing fumarates in the setting of severe and prolonged lymphopenia. PML is an opportunistic infection caused by John-Cunningham virus (JCV), which may be fatal or result in severe disability. PML can only occur in the presence of a JCV infection. If JCV testing is undertaken, it should be considered that the influence of lymphopenia on the accuracy of anti-JCV antibody test has not been studied in Tecfidera treated patients. It should also be noted that a negative anti JCV antibody test (in the presence of normal lymphocyte counts) does not preclude the possibility of subsequent JCV infection.

Prior treatment with immunosuppressive or immunomodulating therapies

No studies have been performed evaluating the efficacy and safety of Tecfidera when switching patients from other disease modifying therapies to Tecfidera. The contribution of prior immunosuppressive therapy to the development of PML in Tecfidera treated patients is unknown. When switching patients from another disease modifying therapy to Tecfidera, the half-life and mode of action of the other therapy should be considered in order to avoid an additive immune effect while at the same time, reducing the risk of reactivation of MS.

A complete blood count is recommended prior to initiating Tecfidera and regularly during treatment (see Blood/laboratory tests above).

Tecfidera can generally be started immediately after discontinuation of interferon or glatiramer acetate.

Infections

In phase III placebo-controlled studies, the incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with Tecfidera or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts $<0.8x10^9$/L or $<0.5x10^9$/L. During treatment with Tecfidera in the MS placebo controlled trials, mean lymphocyte counts decreased by approximately 30% from baseline at one year and then plateaued (see section 4.8). Mean lymphocyte counts remained within normal limits. **Patients with lymphocyte counts $<0.5x10^9$/L were observed in <1% of patients treated with placebo and 6% of patients treated with Tecfidera. In clinical studies (both controlled and uncontrolled), 2% of patients experienced lymphocyte counts $<0.5 \times 10^9$/L for at least six months. In these patients, the majority of lymphocyte counts remained $<0.5 \times 10^9$/L with continued therapy.**

If therapy is continued in the presence of severe prolonged lymphopenia, the risk of an opportunistic infection, including Progressive Multifocal Leukoencephalopathy (PML) cannot be ruled out (please refer to subsection PML above for further details).

If a patient develops a serious infection, suspending treatment with Tecfidera should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Patients receiving Tecfidera should be instructed to report symptoms of infections to a physician. Patients with serious infections should not start treatment with Tecfidera until the infection(s) is resolved.

4.8 Undesirable Effects

Haematological

In the placebo-controlled studies, most patients (>98%) had normal lymphocyte values prior to initiating treatment. Upon treatment with Tecfidera, mean lymphocyte counts decreased over the first year with a subsequent plateau. On average, lymphocyte counts decreased by approximately 30% of baseline value. Mean and median lymphocyte counts remained within normal limits. Lymphocyte counts $<0.5x10^9$/l were observed in <1% of patients treated with placebo and 6% of patients treated with Tecfidera. A lymphocyte count $<0.2x10^9$/l was observed in 1 patient treated with Tecfidera and in no patients treated with placebo.The incidence of infections (58% versus 60%) and serious infections (2% versus 2%) was similar in patients treated with placebo or Tecfidera. An increased incidence of infections and serious infections was not observed in patients with lymphocyte counts $<0.8x10^9$/l or $<0.5x10^9$/l. **PML has occurred in the setting of severe and prolonged lymphopenia (please refer to section 4.4)**. A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.