December 03, 2014

Tecfidera (dimethyl fumarate): Progressive Multifocal Leukoencephalopathy (PML) has occurred in a patient with severe and prolonged lymphopenia.

Dear Healthcare Professional,

In agreement with European Medicines Agency (EMA), Biogen Idec would like to inform you of important safety information regarding a case of PML related to use of Tecfidera in the treatment of multiple sclerosis:

Summary

- **In October 2014, a fatal case of PML, in the setting of severe prolonged lymphopenia, was reported in a patient receiving Tecfidera for 4.5 years. This is the first case of PML associated with Tecfidera. Patients should be informed that there is a risk of this serious condition.**

- **Lymphopenia is a known adverse drug reaction of Tecfidera and patients under treatment should be monitored regularly. Complete blood counts (CBC), including lymphocytes, should be checked regularly and at close intervals as clinically indicated.**

- **Patients receiving Tecfidera who experience lymphopenia should be monitored closely and frequently for signs and symptoms of neurological dysfunction**

- **When PML is suspected Tecfidera should be discontinued immediately.**

Further information

Tecfidera is authorized for treatment of adult patients with relapsing remitting multiple sclerosis. Tecfidera may cause lymphopenia and lymphocyte counts decreased by approximately 30% from baseline values during treatment in clinical trials.

Patients under treatment with Tecfidera should be monitored closely and complete blood counts (CBC), including lymphocytes, should be taken regularly and more frequently as clinically indicated.

A case of PML was reported in October 2014. The patient was participating in the open-label ENDORSE study and received 4.5 years of Tecfidera therapy. During treatment with Tecfidera, the patient experienced severe and prolonged lymphopenia (over 3.5 years of duration). Prolonged lymphopenia may be associated with an increased risk of PML. Lymphocyte counts fluctuated between 200 and 580 cells/µL [predominantly CTC Grade 3 i.e. severe (between 200 and 500 cells/µL) since January 2011].

Biogen Idec Limited
Innovation House 70 Norden Road Maidenhead SL6 4AY United Kingdom Phone +44 (0) 1628 501000 Fax +44 (0)1628 501010
Company Registration Number 1497267

The patient died due to complications associated with the deteriorating neurological conditions and aspiration pneumonia.

PML is a rare and serious brain infection caused by JC virus. This virus is commonly found in the general population but only leads to PML if the immune system has been weakened. PML presents with similar symptoms as multiple sclerosis as it is a demyelinating disease. If the symptoms are suggestive of PML, or if any doubt exists, treatment with Tecfidera should be discontinued and further evaluation should be conducted.

Physicians should inform their patients about the risk of PML appropriately.

This is the first case of PML associated with Tecfidera. In the past, other cases of PML have been reported with the use of fumaric acid esters in lymphopenic patients with psoriasis, although in the majority of these cases, the causal relationship could not be clarified (e.g. other risks for PML were present).

Biogen Idec is currently evaluating available evidence and will work with the EMA to consider appropriate changes to the prescribing information including further guidance on managing severe and prolonged lymphopenia and the risk of PML. Any new advice for healthcare professionals and patients will be communicated promptly.

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, via the Yellow Cards website: www.mhra.gov.uk/yellowcard

Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gsi.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789, or by downloading and printing a form from the Yellow Card section of the MHRA website

ADRs can also be reported to the Marketing Authorisation Holder (MAH) by telephone (0800 008 7401), fax [+44 (0) 1748 828801] or email (biogenidec@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

Dr Fiona Thomas MBChB
Medical Director, UK and Ireland

TF-GBR-0114 Date of Preparation: November 2014

Biogen Idec Limited
Innovation House 70 Norden Road Maidenhead SL6 4AY United Kingdom Phone +44 (0) 1628 501000 Fax +44 (0)1628 501010
Company Registration Number 1497267