NATIONAL PBM BULLETIN

November 7, 2014

DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

DIMETHYL FUMARATE (TECFIDERA) AND PML RESULTING IN DEATH

I. ISSUE

A case of progressive multifocal leukoencephalopathy (PML) has been reported in a patient taking dimethyl fumarate (Tecfidera).

II. BACKGROUND

The FDA has received a report of patient death from the manufacturer of dimethyl fumarate (Tecfidera). The patient was receiving dimethyl fumarate (Tecfidera) and the cause of death is potentially due to PML. The patient was being treated at a facility in Europe and had participated in the placebo arm of the DEFINE trial, one of the pivotal global, randomized, double-blind, placebo-controlled, 2-year Phase III studies. The patient elected to continue into the open extension trial ENDORSE, where treatment allocation is still blinded. Patients may be receiving dimethyl fumarate (Tecfidera) twice or three times daily. The patient had no prior immunosuppression with natalizumab (Tysabri); had 4.5 years exposure to dimethyl fumarate (Tecfidera); and had Grade 3 lymphopenia ($> 0.2 \times 10^9$ /L and $<0.5 \times 10^9$/L) for 3.5 years. The patient displayed symptoms of relapse in July 2014. Imaging and CSF analysis at that time indicated potential PML; however a final diagnosis was not made. The patient expired from aspiration pneumonia. No autopsy was performed. The manufacturer stated that results of PML testing from July 2014 are not known.

III. DISCUSSION

A decrease in lymphocyte counts is an identified risk of dimethyl fumarate (Tecfidera). Severe, prolonged lymphopenia is a known risk factor for PML. According to prescribing information, mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate (Tecfidera) and then remained stable in clinical trials. Mean lymphocyte counts increased but did not return to baseline four weeks after discontinuing treatment. Lymphocyte counts $< 0.5 \times 10^9$/L (lower limit of normal 0.9×10^9/L) occurred in 6% of dimethyl fumarate (Tecfidera) patients and < 1% of placebo patients. There was no increased incidence of serious infections observed in patients with lymphocyte counts $< 0.8 \times 10^9$/L or 0.5×10^9/L. The incidence of infections (60% versus 58%) and serious infections (2% versus 2%) was similar in patients treated with dimethyl fumarate (Tecfidera) or placebo, respectively. A transient increase in mean eosinophil counts was seen during the first 2 months of therapy with dimethyl fumarate (Tecfidera).

IV. PROVIDER RECOMMENDATIONS

As detailed in the VA PBM Dimethyl Fumarate (Tecfidera) Criteria for Use Update March 2014 :

- Before initiating treatment with dimethyl fumarate (Tecfidera), a recent complete blood count (CBC) (i.e. within 6 months) should be available.
- A lymphocyte count below 500/µL (equal to less than 0.5×10^9/L) is an exclusion criteria for initiating therapy with dimethyl fumarate (Tecfidera).
- Dimethyl fumarate (Tecfidera) should be held if the WBC falls below 2000/ µL or the lymphocyte count is below 500/µL and permanently discontinued if the WBC did not increase to over 2000/ µL or lymphocyte count increased to over 500/µL after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored on a quarterly basis.

Providers should continue to report any adverse reactions with the use of dimethyl fumarate (Tecfidera) by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or by mail).

V. REFERENCES

1. Biogen Idec. Data on file.
2. TECFIDERA® (dimethyl fumarate) US Prescribing Information, 41347-02. Cambridge, MA. © Biogen Idec Inc. Mar 2013.

ACTIONS

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS).*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers who prescribe these medications (e.g.,* ***primary care providers, neurology, infectious disease specialists, including contract providers, etc****.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*