

9 יולי, 2015

## **טקפידרה (dimethyl fumarate): מידע בטיחות בנוגע לסיכון ל Progressive Multifocal Leukoencephalopathy (PML) על רקע לימפופניה חמורה וממושכת**

צוות רפואי נכבד,

חברת ביג'ן איידק מעוניינת להודיע לך על מידע בטיחות בנוגע לשני מקרים של PML הקשורים לשימוש בטקפידרה לטיפול בטרשת נפוצה:

### **תקציר**

- באוקטובר 2014, אירע מקרה מוות מ PML על רקע לימפופניה חמורה וממושכת של 3.5 שנים לפחות, בחולה טרשת נפוצה התקפית-הפוגתית (RRMS) אשר נטל טקפידרה במשך 4.5 שנים.
- ביוני 2015, אירע מקרה שני של PML, גם כן על רקע לימפופניה חמורה וממושכת של 18 חודשים לפחות, בחולה טרשת נפוצה מתקדמת-ראשונית (PPMS) אשר נטל טקפידרה במשך כשנתיים וחודשיים. בישראל, טקפידרה מתוות לטיפול בטרשת נפוצה התקפית-הפוגתית (RRMS) ואינה מתוות לטיפול בחולים עם PPMS. נכון לעכשיו, החולה יציב ואיננו מאושפז.
- לימפופניה הינה תופעת לוואי ידועה ושכיחה של טקפידרה, חולים תחת טיפול צריכים להיות מנוטרים בקביעות. ספירת דם מלאה (CBC), כולל לימפוציטים, צריכה להיבדק באופן קבוע ובמרווחים קרובים כמצוין בהתוויה.
- PML הינו זיהום מוחי נדיר וחמור הנגרם על ידי וירוס JC, אשר מתרחש בדרך כלל בחולים עם מערכת חיסונית מוחלשת. PML עלול לגרום לנכות קשה ומוות. חלק מהתסמינים של PML דומים לתסמינים של טרשת נפוצה ויכולים לכלול חולשה בצד אחד של הגוף, תחושת סרבול, בעיות בראיה, בלבול, ושינויים בחשיבה, באישיות, בזיכרון ובהתמצאות. במידה והתסמינים מרמזים על PML, או אם קיים ספק כלשהו, יש להפסיק את הטיפול בטקפידרה ולבצע בירור נוסף. בחולים הנוטלים טקפידרה ופיתחו לימפופניה צריכים להיות במעקב צמוד ולעיתים קרובות אחר סימנים ותסמינים של פגיעה בתפקוד הנוירולוגי.
- כאשר יש חשד ל PML, יש להפסיק טיפול בטקפידרה באופן מיידי.



**Tecfidera (dimethyl fumarate): Safety Information regarding the risk of Progressive Multifocal Leukoencephalopathy (PML) has occurred in setting of severe and prolonged lymphopenia.**

Dear Healthcare Professional,

Biogen Idec would like to inform you of important safety information regarding 2 cases 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 for at least 3.5 years, was reported in a patient with relapsing- remitting multiple sclerosis receiving Tecfidera, for 4.5 years.
- In June 2015, a second case of PML, also in the setting of severe and prolonged lymphopenia for at least 18 months, was reported in a primary progressive multiple sclerosis (PPMS) patient receiving Tecfidera for approximately 2 years and 2 months. In the state of Israel, Tecfidera is indicated in relapsing remitting multiple sclerosis and is not indicated for patients with PPMS. At this time, the patient is stable and is not hospitalized.
- Lymphopenia is a known common 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.
- PML is a rare and serious brain infection caused by JC virus, occurring typically in patients who have weakened immune system. PML can lead to severe disability and death. Some symptoms of PML are similar to those of MS and may include progressive weakness on one side of the body, clumsiness, vision problems, confusion, and changes in thinking, personality, memory, and orientation. If the symptoms are suggestive of PML, or if any doubt exists, treatment with Tecfidera should be discontinued and further evaluation should be conducted. 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. 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.

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.

The first 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/ $\mu$ L [predominantly CTC Grade 3 (between 200 and 500 cells/ $\mu$ L) since January 2011]. The patient died due to complications associated with the deteriorating neurological conditions and aspiration pneumonia.

A second case of PML was reported in June 2015. The patient with PPMS had received approximately 2 years and 2 months Tecfidera therapy. During treatment with Tecfidera, the patient experienced severe and prolonged lymphopenia for at least 18 months. Prolonged lymphopenia may be associated with an increased risk of PML. Lymphocyte counts fluctuated between 300 and 530 cells/ $\mu$ L [predominantly CTC Grade 3 (between 200 and 500 cells/ $\mu$ L) for 18 months. The patient is stable and due to that he was released from the hospital.

PML is a rare and serious brain infection caused by JC virus. This virus is commonly found in the general population and can lead to PML in patients with weakened immune system. Symptoms of PML are diverse, progress over days to weeks, and may include progressive weakness on one side of the body, clumsiness, vision problems, confusion, and changes in thinking, personality, memory, and orientation. The progression of deficits can lead to severe disability or death. 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.

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 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 national requirements via the electronic form found at the following address:

<https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

**Company contact point**

Contact point details for further information are given in the product information of the medicinal product (SmPC and PIL)

