



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Updated recommendations to minimise the risk of the rare brain infection PML with Tecfidera

Related recommendations apply to other fumarate medicines

The European Medicines Agency (EMA) has issued new advice for doctors and patients in order to minimise the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with the multiple sclerosis medicine Tecfidera (dimethyl fumarate). PML is a rare brain infection caused by John Cunningham (JC) virus. This virus is very common in the general population and is normally harmless. However, in persons whose immune system is compromised it can lead to PML, with symptoms that may be similar to those of a multiple sclerosis attack, and it may result in severe disability or death.

So far, 3 cases of PML have occurred in patients treated with Tecfidera who had not been treated before with other medicines known to be associated with a risk of PML. These cases occurred after long treatment in patients who had very low levels of lymphocytes, a type of white blood cell, over an extended period of time. Very low lymphocyte levels are known to develop in a small proportion of patients receiving Tecfidera. EMA started a review of this risk in November 2014, after the first case of PML was reported.

EMA has now recommended that a complete blood count should be performed before starting treatment with Tecfidera, and every 3 months during treatment. Additionally, a baseline MRI should be available (usually within 3 months) as a reference. If during treatment the levels of lymphocytes drop to very low levels for more than 6 months, the doctor should consider stopping Tecfidera. If treatment is continued, patients should be closely monitored (see below under 'Information for healthcare professionals').

EMA also reviewed cases of PML which occurred with two other fumarate-containing medicines, Fumaderm and Psorinovo, used to treat psoriasis. Related recommendations have been issued.

Information for patients

Tecfidera

- The multiple sclerosis medicine Tecfidera can cause low levels of lymphocytes, a type of white blood cell that fights infections. If this happens in patients who have been infected with JC virus they may be less able to fight the virus and could develop a serious brain infection known as progressive multifocal leukoencephalopathy (PML). A very small number of cases of PML have been reported in patients taking Tecfidera who had very low levels of lymphocytes for over 6 months.



- During treatment with Tecfidera, your doctor will perform blood tests on a regular basis to check your white blood cell levels. If during treatment your lymphocyte levels stay at very low levels for more than 6 months, your doctor will speak to you about whether Tecfidera is still the best option for you, and may decide to stop your treatment.

Fumaderm

- Some patients who are being treated with the psoriasis medicine Fumaderm, whose active substances include dimethyl fumarate, the active substance in Tecfidera, may also have persistently low levels of lymphocytes, and so may also be at higher risk of PML if they have been infected with JC virus. Therefore, related recommendations regarding the monitoring of white blood cell levels are being issued for these medicines, based on the evidence available from the case reports of PML received for Fumaderm. Fumaderm is only marketed in Germany.
- If you have any questions or concerns, speak to your doctor or pharmacist.

Information for healthcare professionals

Tecfidera

Lymphopenia is a known and common side effect with Tecfidera. Three unconfounded cases of progressive multifocal leukoencephalopathy (PML) have occurred so far with Tecfidera in the setting of prolonged (over 6 months) severe lymphopenia. PML is an opportunistic infection caused by John-Cunningham (JC) virus, which may result in severe disability or even be fatal.

Having reviewed the available information on the risk of PML, EMA has recommended the following to minimise this risk with Tecfidera:

- Prior to initiating treatment with Tecfidera, a complete blood count including a lymphocyte count should be performed and a baseline MRI scan should be available (usually within 3 months) as a reference. After starting therapy, complete blood counts including lymphocytes should be performed every 3 months.
- If during treatment with Tecfidera the lymphocyte count drops below $0.5 \times 10^9/L$ for more than 6 months, the benefit-risk of continued treatment with Tecfidera should be re-considered in the context of other therapeutic options available. Clinical factors and evaluation of any laboratory and imaging investigations could be included as part of this re-consideration. If Tecfidera is discontinued, the lymphocyte count should be closely monitored until recovery.
- PML can only occur in the presence of JC virus infection. If an anti-JC virus antibody test is done, it should be considered that the influence of lymphopenia on the accuracy of such tests has not been studied in patients treated with Tecfidera. Doctors should also note that a negative antibody test (in the presence of normal lymphocyte counts) does not preclude the possibility of subsequent JC virus infection.
- During treatment with Tecfidera, the need for further MRI scans 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.
- If therapy is continued in patients with severe prolonged lymphopenia, these patients should be considered at increased risk for PML and should be monitored closely for signs and symptoms of new neurological dysfunction (e.g. motor dysfunction, cognitive or psychiatric symptoms).

- In case PML is suspected, treatment with Tecfidera should be withheld immediately and further evaluations performed.
- 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 patients treated with Tecfidera is unknown. When switching patients from other disease-modifying therapy to Tecfidera, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time reducing the risk of disease reactivation.

The product information for Tecfidera will be updated in line with the above recommendations.

Fumaderm

EMA also reviewed cases of PML which occurred with two other fumarate medicines, Fumaderm and Psorinovo, both used to treat psoriasis. Cases of PML have also occurred in patients with prolonged lymphopenia who were treated with these medicines, and the following recommendations are being issued for Fumaderm:

- Before starting treatment, a complete blood count should be performed; in the presence of values outside the normal range, treatment should not be started.
- During treatment, blood cell counts should be monitored every 4 weeks; if the lymphocyte count drops below $0.7 \times 10^9/L$, the dose should be halved. If during a follow-up check after 4 weeks the lymphocyte count remains below this value, then treatment must be discontinued. If therapy is continued in presence of a lymphocyte count below $0.7 \times 10^9/L$, the risk of PML cannot be ruled out.
- If the lymphocyte count drops below $0.5 \times 10^9/L$, treatment should be discontinued.

More about the medicine

Tecfidera is a medicine used to treat adults with multiple sclerosis, a disease in which inflammation destroys the protective sheath around the nerves. Tecfidera is used specifically in adults with relapsing-remitting multiple sclerosis, where the patient has flare-ups of symptoms (relapses) followed by periods of recovery (remissions). Tecfidera contains the active substance dimethyl fumarate.

More information on Tecfidera can be found on [EMA's website](#).

Fumaderm is a nationally-authorized medicine used to treat psoriasis; it contains the active substances dimethyl fumarate and ethyl hydrogen fumarate salts. It is only marketed in Germany. Another psoriasis medicine, Psorinovo, is available as a compounded fumarate preparation in the Netherlands¹.

More about the procedure

This review was conducted by EMA's Committee for Medicinal Products for Human Use (CHMP) in the context of a procedure known as a 'type II variation'. During its assessment, the CHMP sought the advice of a group of experts in neurology, virology and immunology, and from patients' representatives.

¹ This document has been revised to state that Psorinovo is available in the Netherlands. It previously stated that the medicine is available in Germany.

The CHMP opinion will now be sent to the European Commission for a legally binding decision valid throughout the EU.

Contact our press officer

Monika Benstetter

Tel. +44 (0)20 3660 8427

E-mail: press@ema.europa.eu