The United Kingdom: Dimethyl fumarate (Tecfidera): updated advice on risk of progressive multifocal leukoencephalopathy

The Medicines and Healthcare products Regulatory Agency (MHRA) announced that cases of progressive multifocal leukoencephalopathy have been reported in patients taking dimethyl fumarate for multiple sclerosis, who all had prolonged lymphopenia.

Dimethyl fumarate (Tecfidera) is authorised in the UK to treat relapsing-remitting multiple sclerosis. This medicine can cause lymphopenia.

Dimethyl fumarate is associated with an increased risk of PML—a rare, progressive, and demyelinating disease of the central nervous system that can be fatal. It is caused by activation of the JC virus, which usually remains latent and typically only causes PML in immunocompromised patients.

In March 2015, the MHRA informed the public of a fatal case of PML in a patient participating in the open-label ENDORSE study of dimethyl fumarate in multiple sclerosis. In November 2015, the licence-holder sent a letter to health professionals regarding another 2 cases of PML in patients who had been taking dimethyl fumarate for multiple sclerosis. All three patients were male and had not received any other medicines known at the time to be associated with a risk of PML. All three were seropositive for anti-JCV antibodies at the time of PML diagnosis. A 4th confirmed case of PML has also been reported. Summary of the cases can be found at the MHRA website.

The MHRA advised healthcare professionals of the following:

1) Before starting dimethyl fumarate treatment

New advice:

- Perform a baseline cranial MRI scan as a reference, usually within 3 months of starting dimethyl fumarate treatment

Reminder of previous advice:

- Perform a full blood count including lymphocyte subsets
- Counsel patients and carers on the risk of progressive multifocal leukoencephalopathy (PML); advise them on symptoms to watch out for and to get medical help urgently if they occur
- If John Cunningham virus (JCV) testing is undertaken, consider that the influence of lymphopenia on the accuracy of the anti-JCV antibody test has not been studied in patients treated with dimethyl fumarate

2) During dimethyl fumarate treatment

New advice:

- In any patient, if PML is suspected, stop dimethyl fumarate immediately and investigate appropriately, eg MRI scan; ultrasensitive polymerase chain reaction (PCR) assay for JCV DNA
- Monitor full blood count every 3 months
- Consider interrupting dimethyl fumarate if lymphocyte counts fall below $0.5x10^9$/L for more than 6 months
- If treatment is stopped, monitor lymphocyte counts until they return to normal
- Note that patients might still develop a JCV infection, even if they have a normal lymphocyte count and previously tested negative for anti-JCV antibodies

Reminder of previous advice:

- Monitor patients for signs and symptoms or appearance of new neurological dysfunction (eg motor, cognitive, or psychiatric symptoms), bearing in mind that PML can present with features similar to multiple sclerosis

3) If dimethyl fumarate treatment is continued in patients with severe prolonged lymphopenia

New advice:

- Consider further MRI imaging as part of increased vigilance for PML, in accordance with national and local recommendations
- Counsel patients again on the risk of PML and remind them of the symptoms to watch out for signs of PML

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/dimethyl-fumarate-tecfidera-updated-advice-on-risk-of-progressive-multifocal-leukoencephalopathy

In Hong Kong, there are two registered pharmaceutical products containing dimethyl fumarate, namely Tecfidera Gastro-resistant Capsules 120mg (HK-64411) and Tecfidera Gastro-resistant Capsules 240mg (HK-64410) which are registered by UCB Pharma (Hong Kong) Limited. Both products are prescription only medicines. Related news was previously issued by the US FDA, Health Canada, MHRA and EMA, and was posted on the Drug Office website on 26 November 2014, 7 February 2015, 31 March 2015 and 24 October 2015 respectively. So far, the Department of Health (DH) has not received any adverse drug reaction case related to dimethyl fumarate. The package insert of the local products has already included the warning on PML. In view of the above MHRA announcement, letters to local healthcare professionals to draw their attention on the new advice will be issued. DH will remain vigilant on the safety of medicines containing dimethyl fumarate.

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