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New recommendations to minimise risks of the rare brain infection PML and a type of skin cancer with Gilenya

Cases of PML reported in patients who had not been previously treated with immunosuppressive medicines

The European Medicines Agency (EMA) has issued new advice for doctors and patients on the potential risks related to the immunosuppressive effect of the multiple sclerosis medicine Gilenya (fingolimod). In particular, new recommendations are given to minimise the risk of progressive multifocal leukoencephalopathy (PML) and basal cell carcinoma in patients treated with Gilenya.

PML is a rare brain infection caused by John Cunningham (JC) virus, which causes symptoms that may be similar to those of a multiple sclerosis attack, and may result in severe disability or death. Basal cell carcinoma is a slow-growing type of skin cancer which almost never spreads to other parts of the body or becomes life-threatening; however, it can be disfiguring if not treated promptly.

The active substance in Gilenya, fingolimod, reduces the activity of the immune system, in particular of certain cells called T cells. Because T cells are involved in fighting disease and infection, patients treated with Gilenya may be at higher risk of developing infections and diseases, including PML and some types of cancer. So far 3 confirmed cases of PML have been reported in patients treated with Gilenya who had not received previous treatment with natalizumab (another immunosuppressive multiple sclerosis medicine)[1]. In addition, 151 cases of basal cell carcinoma have been reported[2].

EMA has now recommended that patients should be evaluated before and during treatment with Gilenya to allow early identification of signs and symptoms that could be linked to PML or basal cell carcinoma and treat patients accordingly. Before starting treatment with Gilenya, a baseline MRI scan should be available (usually within 3 months) as a reference. If PML is suspected, MRI should be performed immediately and treatment with Gilenya should be suspended until PML has been excluded. With regard to the risk of basal cell carcinoma, a medical evaluation of the skin is recommended before starting treatment, after at least one year and then at least yearly during treatment with Gilenya. Gilenya must not be used in patients with basal cell carcinoma, or any other type of cancer.

[1] 3 confirmed cases of PML have been reported so far in patients treated with Gilenya who had not received previous treatment with natalizumab; 17 suspected cases of PML have been reported in Gilenya patients previously treated with natalizumab.
[2] 151 cases of basal cell carcinoma have been reported worldwide as of 28 February 2015; as of this date, exposure to Gilenya was estimated at approximately 219,000 patient-years. One patient-year is equivalent to 1 patient taking the medicine for 1 year.

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The product information for Gilenya will be updated with information about PML, basal cell carcinoma and other risks associated with the weakening of the immune system, in line with the new recommendations.

Information for patients

- The multiple sclerosis medicine Gilenya reduces the activity of the immune system (the body's natural defences). Because of this, patients treated with Gilenya may be at higher risk of developing infections, including a serious brain infection known as progressive multifocal leukoencephalopathy (PML), and some types of cancer such as basal cell carcinoma (a slow-growing type of skin cancer).
- PML, although rare, is more likely to occur during treatment with Gilenya if patients have been previously treated with another multiple sclerosis medicine that suppresses the immune system such as natalizumab. However, recently there have been 3 cases of PML in patients treated with Gilenya who had not received previous treatment with natalizumab. PML is a serious condition which may result in severe disability or death.
- During treatment with Gilenya your doctor may perform a test such as an MRI scan to monitor your condition; if PML is suspected, your doctor will stop treatment with Gilenya until PML can be ruled out.
- Symptoms of PML may be similar to those of a multiple sclerosis attack. Symptoms might include changes in mood or behaviour, memory lapses, speech and communication difficulties. If you believe your disease is getting worse or if you notice any new or unusual symptoms, speak to your doctor as soon as possible.
- Before starting treatment with Gilenya, and then once a year during treatment, your doctor will also check your skin for any sores, lumps, or damaged areas (lesions) that may appear and might be a sign of cancer; further tests may be needed if lesions are discovered. Talk to your doctor if you notice any skin lesions that do not heal within weeks.
- If you have any questions or concerns, speak to your doctor or pharmacist.

Information for healthcare professionals

Due to its immunosuppressive effects, Gilenya (fingolimod) may predispose to serious adverse reactions. Cases of progressive multifocal leukoencephalopathy (PML), opportunistic infections including infections of the central nervous system, and cancers including basal cell carcinoma have been reported. Cases of PML in patients who were previously treated with immunosuppressive therapy have been reported since marketing authorisation of Gilenya. More recently, 3 confirmed cases of PML have occurred with Gilenya in patients who had not received previous treatment with natalizumab[1].

In light of the available data, EMA is recommending the following:

- Doctors should be alert about the risk of PML with Gilenya, and should inform patients and carers of early signs and symptoms suggestive of PML. Patients should be advised to seek medical advice if they think their disease is getting worse, or if they notice any new or unusual symptoms.
- Before starting treatment with Gilenya, a baseline MRI should be available (usually within 3 months) as a reference. During routine MRI (in accordance with national and local recommendations), physicians should pay attention to lesions suggestive of PML. MRI may be considered as part of increased vigilance in patients considered at increased risk of PML.

- If PML is suspected, MRI should be performed immediately and treatment with fingolimod should be suspended until PML has been excluded.
- 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 fingolimod. Doctors should also note that a negative antibody test does not preclude the possibility of subsequent JC virus infection.
- Cases of basal cell carcinoma (BCC) have been reported in patients receiving fingolimod in the clinical trial programme and the post-marketing period[2]. Gilenya is now contraindicated in patients with BCC.
- Doctors should be vigilant for skin lesions, and a medical evaluation of the skin is recommended before starting treatment, after at least one year and then at least yearly during treatment with Gilenya. Patients should be informed about common potential signs of BCC (skin nodules, patches or open sores that do not heal within weeks) and the need to seek medical advice if they occur. Patients should be referred to a dermatologist if they have lesions suggestive of BCC.

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

More about the medicine

Gilenya is a medicine used to treat adults with multiple sclerosis, a disease in which inflammation destroys the protective sheath around the nerves. It 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). Gilenya is used when the disease has failed to respond to at least one other treatment known as 'disease modifying therapy', or is severe and getting worse rapidly. Gilenya contains the active substance fingolimod.

More information on Gilenya can be found on the EMA's website.

More about the procedure

The review of Gilenya 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.

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

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