# Healthcare Professional Guideline

## Important safety information for Sclera® (dimethyl fumarate)

**Dear Healthcare Professional:**

**Kindly note that the Risk Minimization Activities are approved by Saudi Food and Drug Authority (SFDA).**

### About this guideline

This guideline is intended to inform healthcare professionals about the risk of serious infections, mainly opportunistic infections such as progressive multifocal leukoencephalopathy (PML), associated with the use of Sclera® and to provide guidance on how to minimize and manage this risk through appropriate monitoring of lymphocyte and leukocyte count abnormalities. Sclera® (dimethyl fumarate) is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis. Further information on the dosing, efficacy, and safety of Sclera® is available in the Summary of Product Characteristics (SmPC).

### Progressive Multifocal Leukoencephalopathy (PML)

PML is a rare, opportunistic viral infection of the central nervous system[1], characterized by progressive inflammation and demyelination of the white matter of the brain at multiple locations.2 PML occurs due to reactivation of the John Cunningham virus (JC virus), a human polyomavirus.1 Most humans have been exposed to the JC virus during their lifetimes, and infection usually occurs during the first decades of life. Typical symptoms associated with PML may include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision and changes in thinking, memory and orientation leading to confusion and personality changes.

### Seriousness, severity and reversibility of PML

PML is a severe, life-threatening disease. In cases where immunomodulation can be stopped, the prognosis improves notably, although substantial permanent neurological deficits are still probable.[4]

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## Risk factors for PML

PML is probably caused by a combination of factors. A previous infection with JCV is considered a prerequisite for the development of PML. Risk factors include the following:

- Previous immunosuppressive treatment [3]
- Persistent moderate or severe lymphopenia [3,16]
- Concomitant disorders that affect the immune system inducing immunosuppression or modifying the ability of the immune system to act (including HIV/AIDS, malignant haematological conditions, and certain immune-mediated diseases, such as sarcoidosis and systemic lupus erythematosus)[3]
- Genetic or environmental factors[3]

## Frequency and time to onset

PML is a rare condition. Despite the fact that approximately 50–80% of adults have serologic evidence of prior exposure to JC virus, the incidence of PML is very low.[5,6] In healthy adults, the incidence of PML is below 3 cases per million person-years.[7] PML is usually an opportunistic infection that almost always develops in the context of an immunosuppressed/ immunocompromised patient. In patients with immune mediated inflammatory conditions (rheumatoid arthritis, psoriatic arthritis, psoriasis, juvenile idiopathic arthritis, ankylosing spondylitis and inflammatory bowel disease) and without additional risk factors for PML (e.g. human immunodeficiency virus or malignancy), the incidence is approximately 0.2 cases per 100,000 patients.[2] Among at-risk populations, the incidence is highest in patients infected with HIV, with reports of 1.3 cases per 1000 person-years, the incidence is much lower amongst other at-risk populations.[8]

PML has been related to a number of drugs, besides fumaric acid ester (FAEs).[9,10] The precise magnitude of the risk of PML related to FAEs treatment is not yet known, since few cases have been reported and studies assessing the incidence of PML in these patients are not available.

At the time of approval of Sclera®, no cases of PML had been reported in clinical trials[11] involving Sclera®, but PML has occurred during the treatment with others FAEs for psoriasis[1] and multiple sclerosis (MS).[12,13,14,15]

According to published data, the patients who developed PML while on treatment with FAEs for psoriasis had received FAEs for a minimum period of 1.5 years prior to the development of PML: the median FAE treatment duration was 3 years and the median duration of lymphopenia was 2 years.

## Patient monitoring

**Specific blood monitoring recommendations for Sclera®**

Sclera® may decrease leukocyte and lymphocyte counts.[3] In order to minimize the risk of severe infections and PML, a current complete blood count (including differential blood count) should be available before initiating treatment with Sclera®. Treatment should not be initiated if leukopenia < 3.0 x$10^9$ cells/L, lymphopenia < 1.0 x$10^9$ cells/L or other pathological results are identified.[3]

During treatment, a complete blood count with differential should be performed every 3 months.[3] The blood monitoring frequency should be increased and treatment should be stopped in the following circumstances:

**Table 1**. Blood test monitoring during treatment

| | Monitoring during treatment<br>Action to take in the following circumstances: | |
|---|---|---|
| **Lymphocytes** | ≥1.0x$10^9$ cells/L | **Every 3 months** |
| | <1.0 x $10^9$ cells/L and >0.7 x $10^9$ cells/L | **Monthly**monitoring until values return to ≥1.0x$10^9$ cells/L for 2 consecutive tests |
| | <7.0 x $10^9$ cells/L | Blood test must be **repeated** and if levels are confirmed then **discontinue** treatment |
| **Leukocytes** | <3.0 x $10^9$ cells/L | **Discontinue** treatment |

Information adapted from Sclera® SmPC.

Patients developing lymphopenia, leukopenia or other haematological disorders should be monitored after stopping treatment until their blood count has returned to the normal range.[3]

## Neurological Patient Monitoring

Patients who develop lymphopenia and leukopenia should be monitored for signs and symptoms of opportunistic infections, particularly if suggestive of PML. Typical signs and symptoms associated with PML are diverse and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision and changes in thinking, memory and orientation leading to confusion and personality changes.[3]

## What to tell your patients

- Inform the patient that very rarely, some patients taking similar products have had a serious brain infection called PML.

- Instruct the patient to contact their doctor immediately if they experience any signs or symptoms suggestive of PML, for example: memory loss, trouble thinking, difficulty with walking and/or loss of vision.
- Explain that blood tests should be performed regularly during the treatment and remind them of the importance of attending all scheduled appointments.

## What to do if PML is suspected

If PML is suspected, treatment with Sclera® should be stopped immediately. The patient should be referred to a neurologist or other relevant specialist so that further appropriate neurological and radiological examinations can be performed.[3]

## What to do if other opportunistic infections occur

Other opportunistic infections can also occur. If a patient develops an infection, suspending treatment with Sclera® should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy.[3]

**Call for reporting**

As a reminder, there is a need to report any suspected adverse reactions to the National Pharmacovigilance and Drug Safety Center (NPC):

**Saudi Food and Drug Authority (SFDA)**
**The National Pharmacovigilance Centre (NPC)**
SFDA call center: 19999
Toll free phone: 8002490000
Fax: +966-11-2057662
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa/

Or; **Qualified Person for Pharmacovigilance**
Abdulkareem bin Mubarak
Jazeera Pharmaceutical Industries (JPI)
Email: SAPV@hikma.com
Tel: +966(11) 4173731 Ext: 1086
Mobile: +966 550017554

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