

Healthcare Professional Guideline

Important safety information for Dimethyl Fumarate SPC[®]

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Adverse events should be reported. Reporting forms and information can be found at website: www.sfda.gov.sa/npc email: npc.drug@sfda.gov.sa or SFDA call center : 19999 Adverse events may also be reported Sudair Pharma Company via pharmacovigilance@sudairpharma.com Phone: +966 920001432 ext.107

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 Dimethyl Fumarate SPC[®] and to provide guidance on how to minimise and manage this risk through

appropriate monitoring of lymphocyte and leukocyte count abnormalities.

Dimethyl Fumarate SPC[®] (dimethyl fumarate) is indicated for the treatment of moderate to severe plaque psoriasis in

adults in need of systemic medicinal therapy.

Further information on the dosing, efficacy, and safety of Dimethyl Fumarate SPC[®] is available in the Summary of

Product Characteristics (SmPC).

Progressive Multifocal Leukoencephalopathy (PML)

PML is a rare, opportunistic viral infection of the central nervous system¹, characterised 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.³

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

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 treatment³
- 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 factors³

Frequency and time to onset

PML is a rare condition. Despite the fact that approximately 80–90% 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 Dimethyl Fumarate SPC[®], no cases of PML had been reported in clinical trials involving Dimethyl Fumarate SPC[®], but PML has occurred during the treatment with others FAEs for psoriasis 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.¹

Patient monitoring

Specific blood monitoring recommendations for **Dimethyl Fumarate SPC[®]**

Dimethyl Fumarate SPC[®] may decrease leukocyte and lymphocyte counts.³ In order to minimise the risk of severe infections and PML, a current complete blood count (including differential blood count) should be available before initiating treatment with Dimethyl Fumarate SPC[®]. Treatment should not be initiated if leukopenia $<3.0 \times 10^9$ cells/L, lymphopenia $<1.0 \times 10^9$ 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:

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

Table 1. Blood test monitoring during treatment.
Information adapted from Dimethyl Fumarate SPC® 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 Dimethyl Fumarate SPC[®] 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 Dimethyl Fumarate SPC[®] should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy.³

References

1. Balak DMW., Hajdarbegovic E, Bramer WM, Neumann MHA and Thio HB. Progressive multifocal leukoencephalopathy associated with fumaric acid esters treatment in psoriasis patients. *J Eur Acad Dermatol Venereol*. 2017.
2. Bharat A, Xie F, Baddley JW et al. Incidence and Risk Factors for Progressive Multifocal Leukoencephalopathy Among Patients With Selected Rheumatic Diseases. *Arthritis Care Res (Hoboken)*. 2012; 64: 612-615.
3. Almirall S.A. Skilarence gastro-resistant tablets Summary of Product Characteristics.
4. Bruce Brew, Nicholas Davies, et al. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. *Nat Rev Neurol*. 2010 Dec;6(12):673.
5. Khalil K, White MK, Lublin F, Ferrante P, Berger JR. Reactivation of JC virus and development of PML in patients with multiple sclerosis. *Neurology*. 2007 ;68:985-990.
6. Egli A, Infanti L, et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. *J Infect Dis*. 2009 ;199(6):837-46.
7. Van Scheependom J, Gielen J, Laton J, Nagels G. Assessing PML risk under immunotherapy: if all you have is a hammer, everything looks like a nail. *Mult Scler* 1352458515596458, first published on July 21, 2015.
8. Amend KL, Turnbull B, Foskett N, Napalkov P, Kurth T, Seeger J. Incidence of progressive multifocal leukoencephalopathy in patients without HIV. *Neurology* 2010; 75: 1326-1332
9. Maas RP PWM, Muller-Hansma AHG, Esselink RAJ, et al. Drug-associated progressive multifocal leukoencephalopathy: a clinical, radiological, and cerebrospinal fluid analysis of 326 cases. *Journal of Neurology*. 2016;263(10):2004-2021
10. Melis M, Biagi C, Småbrekke L, et al. Motola D. Drug-Induced Progressive Multifocal Leukoencephalopathy: A Comprehensive Analysis of the WHO Adverse Drug Reaction Database. *CNS Drugs*. 2015 ;29(10):879-91. doi: 10.1007/s40263-015-0286-3
11. Mrowietz U, Szepietowski J, Loewe R, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: A randomised, double-blind, Fumaderm[®] and placebo-controlled trial (BRI DGE). *Br J Dermatol* 2016.
12. Baharnoori M, Lyons J, Dastagir A, Koralnik I, Stankiewicz JM. Nonfatal PML in a patient with Multiple Sclerosis treated with Dimethyl Fumarate. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e274.
13. Hughes S. Fourth PML Case with Tecfidera in MS calls for vigilance. *Medscape Medical News*. 2015 Dec 17. http://www.medscape.com/viewarticle/856148#vp_1
14. Lehmann-Horn K, Penkert H, Grein P, et al. PML during dimethyl fumarate treatment of multiple sclerosis: how does lymphopenia matter? *Neurol* 4(87;2016):e-pub ahead of print.
15. Rosenkranz T, Novas, M, Terbord, C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. *NEJM*. 2015;372:1476-78.
16. Reich K, Thaci D, Mrowietz U, Kamps A, Neuberther M and Luger T. Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis – A retrospective study (FUTURE). 2009. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*, 610–603 :7

