Healthcare Professional Guideline

Safety information for Skilarence® (dimethyl fumarate)

Reporting suspect adverse reactions after authorisation of the medicinal product is important. It allows continuing monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions to HPRA Pharmacovigilance: website, www.hpra.ie.

Adverse reactions should also be reported to Almirall Limited by email to Almirall@EU.ProPharmaGroup.com

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 Skilarence®, and to provide guidance on how to minimize and manage this risk through appropriate monitoring of lymphocyte and leukocyte count abnormalities.

Skilarence® (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 Skilarence® 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 the infection usually occurs during the first decades of life.

Typical symptoms associated with PML may include progressive weakness on one side of the body, clumsiness of limbs, disturbance of vision, changes in thinking, or in memory and orientation, which can lead to confusion and personality changes.[3]

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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 treatment[3]
- Persistent moderate or severe lymphopenia[3,8]
- Concomitant disorders that affect the immune system, modifying its ability to act properly, or inducing immunosuppression (including HIV/AIDS, malignant haematological conditions, and certain immune-mediated diseases, such as sarcoidosis and systemic lupus erythematosus)[2,9]
- Genetic or environmental factors[3]

Frequency and time to onset

PML is usually an opportunistic infection that almost always develops in the context of an immunosuppressed/immunocompromised patient. Although JCV seroprevalence increases with age and reaches 90% in adults, PML is a rare condition[10, 11]. 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., HIV/ AIDS or malignancy), the reported 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 0.8 cases per 1,000 person-years.[12]

Increased risk of PML has been related to several drugs.[5, 6] According to published data, patients who developed PML while on treatment with fumaric acid esters (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.[8]

At the time of Skilarence® approval, no cases of PML had been reported in clinical trials involving Skilarence®.[7] However, PML has occurred during treatment with others FAEs for psoriasis[1] and with dimethyl fumarate for multiple sclerosis (MS), with an estimated reporting rate of 1.07 cases per 100,000 person-years of post-marketing exposure in MS patients.[13]

Cases of PML have been reported in the post-marketing setting for Skilarence®. These cases occurred in patients older than 70 years being treated with Skilarence, and one with associated moderate lymphopenia and previous therapy with FAEs for 8 years.[11]

Patient monitoring

Specific blood monitoring recommendations for Skilarence®

Skilarence 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 Skilarence®. Treatment should not be initiated if leukopenia < $3.0x10^9$/L, lymphopenia <$1.0x10^9$/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 the treatment should be stopped in the following circumstances:

Monitoring During Treatment		
	Action to take in the following circumstances	
Lymphocytes	≥$1.0 x10^9$ cells/L	Continue monitoring **every 3 months**
	<$1.0 x10^9$ cells/L and ≥ $0.7 x10^9$ cells/L	**Monthly** monitoring until values return to ≥$1.0 x10^9$ cells/L for 2 consecutive tests
	< $0.7 x10^9$ cells/L	Blood test must be **repeated** and if levels are comfirmed then **discontinue** treatment
Leukocytes	< $0.3 x10^9$ cells/L	Discontinue treatment

Further information can be found in the SmPC. Lymphocytes and leukocytes are monitored based on a complete blood count including differential.

Patients developing lymphopenia, leukopenia or other haematological disorders should be monitored after stopping treatment until their blood count has returned to within 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 Skilarence®, or similar products, have experienced 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, weakness of a body side, confusion, personality changes 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 Skilarence® should be stopped immediately. The patient should be referred to a neurologist or other relevant specialist so that further appropriate neurological and imaging examinations can be performed.[3]

What to do if other opportunistic infections occur

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

References

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