Oxford University Hospitals NHS
NHS Trust

NHS
Oxfordshire
Clinical Commissioning Group

Treatment monitoring protocol for Dimethyl fumarate therapy in active Relapsing Remitting Multiple Sclerosis

This protocol provides monitoring guidance for adult patients requiring Dimethyl fumarate therapy in active Relapsing Remitting Multiple Sclerosis. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF

For the multiple sclerosis (MS) Disease Modifying Drugs (DMDs), we are aware of the complexity of drug prescription and monitoring that is required. Therefore, this shared care protocol differs from the standard template used for other non-MS drugs in that the MS service will remain solely responsible for the prescribing and monitoring. However, given the frequency of monitoring required for some drugs, it would be in the best interest of patients if they could have their blood and urine collected at their local GP surgery with the results reported back to the MS Service in Oxford. To facilitate this, we provide a comprehensive guide with regards to the medication being administered and monitoring protocols.

Shared Care Responsibilities

GPs are requested to arrange collection of bloods at the frequency outlined above and report results to the MS service at OUH. For blood tests processed at the OUH lab, the MS team will be able to view blood results on case notes or the electronic patient record.

A) Aspects of care for which the Hospital MS specialist team is responsible:

- Provide the patient with a Tecfidera, Patient guide and the Package Leaflet.
- Ensure the patient understands the nature and complications of drug therapy and their role in reporting adverse effects promptly.
- Counsel patients and carers on the risk of PML, the possible clinical symptoms to be aware of and actions to take if any of these symptoms arise.
- Ensure baseline tests are conducted and reviewed as outlined prior to treatment.
- Prescribe dimethyl fumarate.
- Write to the GP requesting shared care and outline shared care protocol criteria.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform the GP of patients who do not attend clinic appointments.
- Be available to give advice to the GP and patient/carer.
- Be responsible for any out of range blood result as detailed in Appendix Tables 1 & 2

B) Aspects of care for which the GP is responsible:

- Collect bloods for LFT, FBC, and creatinine every 3 months, refer back to specialist if any of the results are out of range (see appendix tables 1 and 2)
- Advise the Hospital Consultant of any clinical changes or adverse effects, where appropriate.
- Request advice from the hospital specialist when necessary.

C) Aspects of care for which the Patient is responsible:

- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Attend their scheduled clinic and blood test appointments.

Written by*: Dr Gabriele De Luca (Consultant Neurologist) and Olivia Moswela (Clinical Pharmacist; Neurosciences)*
Verified by: *The Oxford University Hospitals Multiple Sclerosis Team*
Approved by APCO March 2020. Minor amendment of email contact details: February 2023.

- Report symptoms of infections to the GP / MS specialist.
- Inform other clinical staff that they are receiving treatment with dimethyl fumarate.
- Report any adverse effects to the GP or MS specialist.
- Seek advice from their GP, hospital specialist or pharmacist before purchasing any medication not prescribed by their doctor, including herbal or homeopathic medication.
- Report side effects.
- Female patients of child bearing potential should use effective contraception measures during treatment with dimethyl fumarate.

Background

Dimethyl fumarate and its active metabolite monomethyl fumarate, promote a shift of cytokine patterns from predominantly pro-inflammatory cytokines to predominantly anti-inflammatory cytokines.

Indication

Dimethyl fumarate is recommended as a possible treatment for people with active relapsing-remitting multiple sclerosis that is not highly active or rapidly evolving severe relapsing-remitting multiple sclerosis (NICE Technology Appraisal 320).

Prescribing Information

Dimethyl fumarate will be prescribed by an MS specialist.

Initial dose of 120mg twice a day increased after 7 days to 240mg twice a day.

Patients should be advised to take the dose with food to minimise the incidence of flushing and gastrointestinal adverse effects.

Low dose aspirin (e.g. 75mg), taken 30 minutes before the dose of dimethyl fumarate may help reduce the incidence and severity of flushing associated with dimethyl fumarate. However, long-term use of aspirin is not recommended for the management of flushing.

Patients who do not tolerate the initial dose increase due to flushing and/or gastrointestinal adverse effects despite taking the above measures may benefit from a temporary dose reduction to 120mg twice a day during the first month of treatment. However, the licensed dose for long-term treatment is 240 mg twice a day.

Adverse Effects

The adverse effects listed below are given as a guide only. These MUST be read alongside the summary of product characteristics.

The most frequently reported adverse effects are flushing, hot flushes and gastrointestinal adverse effects (abdominal pain, diarrhoea, nausea and vomiting). These adverse effects are most common during the first month of treatment.

- Elevated hepatic transaminases (ALT or AST) have been reported, primarily during the first six months of treatment.
- Lymphopenia: A decrease in mean lymphocyte counts over the first year with a subsequent plateau has been reported in MS patients treated with dimethyl fumarate. On average, lymphocyte counts decreased by approximately 30% of baseline value.

Written by*: Dr Gabriele De Luca (Consultant Neurologist) and Olivia Moswela (Clinical Pharmacist; Neurosciences)*
Verified by: *The Oxford University Hospitals Multiple Sclerosis Team*
Approved by APCO March 2020. Minor amendment of email contact details: February 2023.

- Progressive Multifocal Leukoencephalopathy (PML) has been reported in the setting of severe and prolonged lymphopenia (defined as <0.5 x 109/L for 6 consecutive months). PML is an opportunistic infection caused by John-Cunningham virus (JCV), which may be fatal or result in severe disability.
- Ketonuria, proteinuria, leucopenia, dyspepsia, gastritis, pruritus, rash, erythema, and burning sensation have also been reported.

Cautions

- Hepatic or renal impairment
- Lymphopenia
- Severe active gastrointestinal disease
- When switching patients from another disease modifying therapy to dimethyl fumarate, the half-life and mode of action of the other therapy should be considered in order to avoid an additive immune effect while at the same time, reducing the risk of reactivation of MS.
- If a patient develops a serious infection, suspending treatment with dimethyl fumarate should be considered.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in the summary of product characteristics.

Pregnancy and Lactation

- Treatment with dimethyl fumarate is not recommended during pregnancy. Women of childbearing age should be advised to use effective contraception during treatment with dimethyl fumarate.

- It is unknown whether dimethyl fumarate or its metabolites are excreted in human milk. A risk to infants cannot be excluded.

Drug Interactions

- Concurrent therapy with nephrotoxic medicinal products (such as aminoglycosides, diuretics, NSAIDs or lithium) may increase the potential of renal adverse reactions in patients taking dimethyl fumarate.

- Live vaccines might carry an increased risk of clinical infection and should not be given to patients treated with dimethyl fumarate unless, in exceptional cases, this potential risk is considered to be outweighed by the risk to the individual of not vaccinating.

Monitoring Standards:

Baseline tests

- Urinalysis (urine dipstick test or send a 2-3ml midstream urine sample to the lab for microscopy without culture)
- Full blood count (FBC) with differential
- Liver function tests (AST or ALT, bilirubin)
- Electrolyte screen (U&E) including serum creatinine

Written by*: Dr Gabriele De Luca (Consultant Neurologist) and Olivia Moswela (Clinical Pharmacist; Neurosciences)*
Verified by: *The Oxford University Hospitals Multiple Sclerosis Team*
Approved by APCO March 2020. Minor amendment of email contact details: February 2023.

- Varicella Zoster (VZV) IgG (if negative, vaccination recommended 6 weeks prior to starting treatment)
- Ensure patients have completed local immunisation requirements 4-weeks prior to starting treatment for non-live vaccines and 6-weeks prior to treatment for live vaccines.
- Pregnancy test, if appropriate
- Baseline MRI within 3 months of starting treatment

On-going treatment safety monitoring (all results to be tracked by MS Service at OUH Mailto ouh.ms@nhs.net**)**

a) Blood studies (every 3 months) – to be collected at OUH or local GP surgery

- Full blood count (FBC) with differential
- Liver function tests (AST or ALT, bilirubin)
- Electrolyte screen (U&E) including serum creatinine

b) Urine studies (every 12 months) – to be collected at OUH only

- Urinalysis (urine dipstick test or send a 2-3ml midstream urine sample to the lab for microscopy without culture)

CONTACTS

MS Advice	Tel 01865 234461 ouh.ms@nhs.net
MS Team Secretaries	Tel 01865 231899 Tel 01865 231896
Neurology Registrar on call John Radcliffe Hospital	Hospital switchboard: 01865 741166 Bleep Registrar on call
Medicines Information	Tel 01865 221505

Written by*: Dr Gabriele De Luca (Consultant Neurologist) and Olivia Moswela (Clinical Pharmacist; Neurosciences)*
Verified by: *The Oxford University Hospitals Multiple Sclerosis Team*
Approved by APCO March 2020. Minor amendment of email contact details: February 2023.

APPENDIX – Blood and Urine monitoring protocol (for information only)

Table 1: On-going Treatment Course Safety Monitoring (blood monitoring)

Every three months	Advice if result out of range
Full blood count with differential (including lymphocytes)	GP to refer to hospital specialist (below protocol for information only): a) Lymphocytes • *If persistent lymphocyte count < 0.5x10^9/L for > 6 months, dimethyl fumarate should be discontinued due to risk of PML.* • *If treatment is discontinued due to lymphopenia the lymphocyte count should be closely monitored until recovery.* If treatment is continued in patients with severe prolonged lymphopenia, enhanced vigilance for PML is recommended: • *Counsel patients and carers again regarding the risk of PML in the presence of risk factors and remind them of the early clinical symptoms to be aware of.* • *Monitor patients for signs and symptoms or appearance of new neurological dysfunction (e.g. motor dysfunction, cognitive or psychiatric symptoms).* • *Consider that PML can present with similar features to those of multiple sclerosis because both are demyelinating diseases* • *As part of increased vigilance for PML, MRI brain scans without contrast to be obtained every six months.* • *If PML is suspected, stop treatment with dimethyl fumarate immediately and investigate appropriately. MRI brain and lumbar puncture for JCV should be performed immediately for diagnostic confirmation.* b) Neutrophils* • *If neutrophil count between 1.0 – 2.0 x 10^9/L, repeat every 4 weeks* • *If neutrophil count < 1x10^9/L, consider stopping dimethyl fumarate* c) Platelets* • *If < 75 x 10^9/L, monitor closely* • *If < 50 x 10^9/L, consider stopping dimethyl fumarate* d) Hemoglobin* • *If < 80 g/L, consider stopping dimethyl fumarate* **exclude other causes*
Liver function test (AST or ALT)	GP to refer to hospital specialist (below protocol for information only) *If an increase of up to 2.5 times the upper limit of normal, repeat monthly. ** *If an increase of greater than 2.5 times the upper limit of normal, consider stopping dimethyl fumarate.** **exclude other causes*
Urea and electrolytes incl. serum creatinine	See Appendix Table 2: Monitoring for Nephropathies

Written by*: Dr Gabriele De Luca (Consultant Neurologist) and Olivia Moswela (Clinical Pharmacist; Neurosciences)*
Verified by: *The Oxford University Hospitals Multiple Sclerosis Team*
Approved by APCO March 2020. Minor amendment of email contact details: February 2023.

Table 2

Monitoring for Nephropathies: ***Yearly Urinalysis with Microscopy and Serum Creatinine (SCr) every 3 Months***

Result		Action
Urine negative for Blood and Protein	Normal SCr	*Continue monitoring*
	Abnormal SCr (or if baseline is abnormal, increase of more than 25%)	*Consider referral to nephrologist*
Urine negative for Blood Positive for Protein and/or WBC	Normal SCr	*Treat UTI if indicated* *Consider referral to nephrologist*
	Abnormal SCr (or if baseline is abnormal, increase of more than 25%)	*Consider referral to nephrologist*
Urine positive for Blood	Abnormal SCr	*Consider urgent referral to nephrologist*
	Normal SCr but >50% increase from baseline	*Consider urgent referral to nephrologist*
	Normal SCr but <50% increase from baseline	*Repeat tests in 2-3days.* • *If blood persists refer to nephrologist* • *If there is no blood and SCr is stable, resume routine monitoring*
	Normal SCr with no increase from baseline	*Weekly Urinalysis with Microscopy & SCr for up to 3 weeks.* • *If at anytime blood clears and SCr is normal, resume routine monitoring* • *If microscopic haematuria persists, refer to nephrologist*

*Morning urine preferred; false positive rate high during menses and one week later. If monthly urinalysis is positive for blood, SCr is normal and the patient is menstruating, the urinalysis should be repeated one week following menses. If the patient has chronic haematuria or proteinuria that is being evaluated or already adequately evaluated, surveillance should focus on changes in these levels and on SCr.

Written by*: Dr Gabriele De Luca (Consultant Neurologist) and Olivia Moswela (Clinical Pharmacist; Neurosciences)*
Verified by: *The Oxford University Hospitals Multiple Sclerosis Team*
Approved by APCO March 2020. Minor amendment of email contact details: February 2023.