What is dimethyl fumarate and how does it work?
Dimethyl fumarate (DMF, Tecfidera, BG-12) was approved by the US FDA in March 2013 as an oral disease modifying treatment for relapsing forms of MS. Combined data from a Phase II study and two Phase III trials showed that DMF reduces relapses, disability progression, MRI lesion activity.

The exact mechanism of action of DMF is not known, but may include direct inhibition of proinflammatory pathways and effects on dendritic cell differentiation. DMF may also act through the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) antioxidant response pathway.

How is DMF administered?
DMF is administered as a single 240mg capsule, twice per day (once in the morning and once in the evening; it does not need to be taken exactly 12 hours apart). A seven-day starter-pack of 120 mg capsules twice per day is available and recommended to help improve tolerability. Food does not alter DMF’s absorption. Therefore, DMF can be taken without regard to meals, although gastrointestinal tolerability may be improved by taking it with food. Missed doses should be skipped and do not need to be made up.

For whom should DMF be considered?
DMF was approved to treat relapsing forms of MS. DMF is also an appropriate treatment option for patients with ongoing disease activity, intolerable side effects, or logistical issues with other MS therapies.

May DMF be used as initial MS therapy?
DMF is approved as first line therapy (i.e. patients are not required to have tried other medications before DMF), although long-term experience with its use is limited.

Should patients switch from a previously-available injected medication to DMF?
We anticipate many patients currently on an injectable therapy will be attracted to DMF’s oral route of administration. However, if a patient is stable clinically and radiographically, and he/she is not experiencing significant adverse effects, in general, we recommend not switching therapy.

For JC virus antibody-positive patients on Tysabri who are concerned about the risk of progressive multifocal leukoencephalopathy, DMF is a reasonable consideration.

What side effects and safety issues does DMF have?
DMF is generally safe and well tolerated. DMF typically lowers the lymphocyte count. The FDA recommends a complete blood count prior to initiating treatment, and then again annually and when clinically indicated.

The main side-effects of DMF are skin flushing and gastrointestinal symptoms.

Skin flushing: Although uncommon, when it is seen, skin flushing typically occurs 30 min to several hours after taking DMF. Pruritis and erythema are sometimes reported, too. A placebo-controlled study found that aspirin can significantly reduce flushing.

Gastrointestinal symptoms: diarrhea, nausea, abdominal pain, vomiting can be seen between 30 min and several hours after taking DMF. Symptoms are most common in the first few weeks after starting DMF, and typically reduce significantly by one month of treatment. Symptomatic therapies can be used in patients, where needed, including H2/proton pump inhibitors, metoclopramide, bismuth subsalicylate, loperamide, as needed depending upon the gastrointestinal symptoms. The enteric

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formulation of DMF makes it mostly like to be absorbed in the intestines. Accordingly, patients who have received gastric bypass are not expected to have altered tolerability.

Although DMF is a potent immunomodulatory drug and reversibly lowers blood lymphocyte counts, the clinical trials did not observe an increased rate of either routine infections or opportunistic infections. However, there are reports of progressive multifocal leukoencephalopathy (PML) with another fumaric acid preparation (Fumaderm), which is available in Germany.

How long should a patient wait after stopping another disease modifying therapy before starting DMF? 
There is no data regarding optimal wash-out times. The theoretical increased risk of complications from incomplete wash-out from the previous therapy needs to be balanced against the risk of return of MS disease activity during a wash-out period. In some patients, the return of disease activity can be very severe. Decisions regarding wash-out are influenced by the treatments and the patients underlying disease activity.

We have adopted the following wash-out periods before starting DMF:
- Interferon, glatiramer acetate, and teriflunomide: no washout
- Fingolimod: 2-3 week wash-out (so that lymphocyte counts normalize)
- Natalizumab: 0-2 months wash-out, depending upon patient characteristics (less wash-out for those with more aggressive disease)
- Corticosteroids: no washout

What testing is required prior to DMF therapy? 
Prior to therapy, a complete blood count (CBC) is recommended.

Are there any restrictions on who can take DMF? 
There are no contraindications for using DMF. Patients with nausea and diarrhea at baseline should use DMF with caution, as it may aggravate those symptoms.

What testing is required during DMF therapy? 
During therapy, a complete blood count is recommended annually. DMF is known to decrease peripheral lymphocyte counts, and some patients can develop very low lymphocyte counts. The relationship between low lymphocyte count and infections is not well understood, so clinical judgment should be used in patients with very low lymphocyte counts.

Does DMF need to be stopped for surgery? 
There are no reports of complications related to surgery in patients receiving DMF, so we do not recommend stopping DMF for surgery.

Does the risk of infection relate to peripheral blood white blood cell or lymphocyte counts? 
There is no clear relationship between the level of lymphocyte reduction and the incidence (or severity) of infections. Therefore, monitoring blood counts is not recommended to assess the risk of infection, but may be useful to monitor for toxicity.

Is DMF effective in progressive MS? 
The effectiveness and safety of DMF in primary and secondary progressive MS is not known.

Is DMF safe during pregnancy? 
Based on animal studies, DMF potentially causes fetal harm and is classified as Pregnancy Category C. Women should use effective contraception while taking DMF and for some time after stopping it. Women should discontinue DMF prior to attempting to become pregnant. There is no known effect of DMF on sperm.

Can DMF be used in combination with other MS disease therapies? 
There are no data concerning the safety or utility of combining DMF with other MS disease therapies. Co-administration of DMF with immunosuppressant medications would be expected to increase the risk of infection.

Can DMF be combined with MS symptom medications? 
DMF can be combined with MS symptom medications without problem. There are no known contraindications between DMF and other medications.

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Can DMF be combined with medications for other conditions?
There are no medications known to interact with DMF.

Can the dose of DMF be increased beyond 240 mg twice daily?
The approved dose of DMF is 240 mg twice daily (480 mg total per day). 240 mg thrice daily (720 mg total per day) were tested in the DMF Phase II and Phase III trials, but there was no greater efficacy at this dose. Lower doses of DMF (i.e. 240 mg once daily) have not been evaluated and so are not currently recommended.

REFERENCES