ALEMTUZUMAB (LEMTRADA™) – CLINICIAN INFORMATION
December 2014

What is the medication?
Generic: alemtuzumab
Brand name: Lemtra™

Has the medication received US Food and Drug Administration (FDA) approval? If so, what are the indications and uses?
Yes. On November 14, 2014, the FDA approved alemtuzumab for treatment of relapsing forms of multiple sclerosis (MS). Because of its safety profile, alemtuzumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

What were the findings in the pivotal and supportive trials of this medication?
Two Phase III trials were performed comparing intravenous alemtuzumab with subcutaneous interferon beta-1a (Rebif) 44 mcg tiw. One of these was done in a treatment-naïve MS population, and the other was in MS patients who had breakthrough disease on another disease-modifying therapy (DMT) for MS. Both studies were published in The Lancet on November 24, 2012.

CARE-MS I trial (Cohen JA et al, 2012)
Trial design: This 2-year randomized, rater-blinded trial compared alemtuzumab 12 mg with subcutaneous interferon beta-1a (Rebif) 44 mcg tiw in 581 treatment-naïve MS patients. Patients were 18 to 50 years old, with an Expanded Disability Status Scale (EDSS) of 3.0 or less, who had at least two relapses within the past 2 years, at least one relapse within the past year, and an abnormal brain MRI consistent with MS. Given the very different side-effect profiles and route/frequency of administration of the two drugs, only the neurologic rater was blinded to the treatment assignment.

Results: Relapse rate and 6-month sustained disability progression were the co-primary endpoints for the CARE-MS I study. Relapses were defined as new or worsening neurologic symptoms due to MS occurring in the absence of fever, lasting over 48 hours, occurring after 30 days of neurologic stability, and causing new findings on neurologic examination. A blinded relapse adjudication committee confirmed relapses.
In CARE-MS I, there was a 54.9% relative reduction (p<0.001) in the relapse rate in the alemtuzumab arm (0.18) compared with the interferon arm (0.39). Sustained disability progression was defined as an increase in EDSS by 1 point (or 1.5 points if initial EDSS was zero) that persisted for 6 months. Eleven percent of patients on interferon beta-1a had sustained disability progression, while only 8% of patients on alemtuzumab had sustained progression; however, this difference was not statistically significant. The alemtuzumab group had fewer patients with new or enhancing lesions on MRI; this effect was greater in the second year of the study. Patients on alemtuzumab also had less brain volume loss on MRI, and both groups had a slight improvement in the EDSS disability score. Thirty-nine percent of the patients receiving alemtuzumab had freedom from clinical and radiographic disease activity, while only 27% of patients in the interferon arm did.

CARE-MS II trial (Coles AJ et al, 2012)

Trial design: This 2-year randomized, rater-blinded trial compared alemtuzumab 12 mg with subcutaneous interferon beta-1a in 667 MS patients who experienced breakthrough disease after 6 months of being on another DMT (primarily interferon-beta or glatiramer acetate). Patients were between 18 and 55 years of age with an EDSS of 5.0 or lower who had at least two relapses within the past 2 years, at least one relapse within the past year, and an abnormal brain MRI consistent with MS. As above, only the neurologic rater was blinded to treatment assignment due to the very different side-effect profiles and route/frequency of administration of the drugs.

Results: Relapse rate and 6-month sustained disability progression were coprimary endpoints for the CARE-MS II study. Relapses were defined as above and were confirmed by a blinded relapse adjudication committee. In CARE-MS II, there was a 49.4% relative reduction in the relapse rate in the alemtuzumab arm (annual rate of 0.26 vs 0.52, p<0.0001) compared with the interferon arm. Sustained disability progression was defined as an increase of EDSS by 1 point (or 1.5 points if initial EDSS was zero) that persisted for 6 months. The alemtuzumab group had a 42% reduction (p=0.0084) in sustained disability progression compared with the interferon group. The alemtuzumab group had fewer patients with new or enhancing lesions on MRI; this effect was greater in the second year of the study. Measurements of new MRI lesions, gadolinium-enhancing lesions, and brain volume also favored alemtuzumab. The alemtuzumab group had a mild improvement in EDSS, while the interferon group declined somewhat on this scale. More patients in the alemtuzumab arm (32% vs 14%) were free of clinical and radiographic disease activity.
What is the mechanism of action and the rationale for the use in MS?

Alemtuzumab is a monoclonal antibody recognizing CD52, which is highly expressed on the surface of certain immune cells (B lymphocytes and T lymphocytes) that are felt to be involved with the pathogenesis of MS. Binding of the antibody to its target causes rapid destruction of the cells expressing CD52, at least those in the vascular compartment; seemingly, this includes destruction of those antireactive lymphocytes that are causing the damage in MS. One study (Jones JL et al 2010) suggests that alemtuzumab may increase the production of neurotrophic factors, perhaps allowing a protective or restorative effect.

What is the delivery route and recommended dosing?

Alemtuzumab is given as an intravenous infusion of 12 mg over at least 4 hours. The initial course is given over 5 consecutive days; the second course is given for 3 consecutive days 1 year later. Subsequent 3-day courses can be given not more frequently than annually for breakthrough disease. The medication can be prescribed only by providers and dispensed by pharmacies enrolled in the Lemtrada REMS (Risk Evaluation and Mitigation Strategy) program. Premedication before the infusions and antiviral prophylaxis are required as described below.

Can this medication be used with other medications?

- Disease-Modifying Therapies (DMTs):
  No studies using alemtuzumab in combination with other MS DMTs have been published.
- Other Medications:
  Currently, studies have not identified any specific concerns regarding the use of alemtuzumab with symptomatic medications commonly used in MS patients.

How does the expected treatment effect compare with the treatment effect provided by other available medications?

The studies with alemtuzumab demonstrate superiority over subcutaneous interferon-beta 1a, which may suggest superiority over other interferon beta formulations, although these studies have not been performed. Other head-to-head studies comparing alemtuzumab with other MS DMTs also have not been performed, so a data-driven comparison regarding the comparative effect of alemtuzumab and other MS DMTs is not possible.
What are the possible short-term side effects? What is the range of severity of side effects, and what are the recommended management strategies?

Over 90% of patients receiving alemtuzumab in the clinical trials experienced infusion reactions – most of which were deemed mild to moderate – typically consisting of skin rash, fever, headache, muscle aches, and temporary reoccurrence of previous neurologic symptoms. More serious but uncommon infusion reactions included anaphylaxis and heart rhythm abnormalities. Pre-infusion treatment typically consisted of high-dose intravenous steroids (required for the first three doses of each treatment course), antihistamines such as famotidine (Pepcid) and/or diphenhydramine (Benadryl), and acetaminophen (Tylenol).

Adverse reactions with incidence >10% and > interferon-beta 1a included rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper-respiratory tract infection, herpes viral infection, urticaria, pruritis, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting.

Alemtuzumab causes immediate and significant depletion of a class of immune cells called lymphocytes. It is advised that vaccinations be up-to-date before starting alemtuzumab. Herpes simplex and zoster infections were more common in the patients who received alemtuzumab in the clinical trials, especially soon after the infusions; therefore, an antiviral medication (like valacyclovir) is recommended for at least 2 months following the first infusion of each treatment course (or until CD4+ lymphocyte count is ≥200 cells/mL).

What are the known long-term (morbidity and mortality) health risks?

Because alemtuzumab causes long-lasting immune suppression, a potentially increased risk of infection exists long after the drug is infused. A subset of lymphocytes called T cells takes years to recover after a patient receives alemtuzumab, while B lymphocytes recover more quickly. This perturbation of the immune system can also lead to eventual autoimmune disease and malignancy.

The most common autoimmunity after alemtuzumab was thyroid autoimmunity, which occurred in about a third of patients receiving the drug in the clinical trial program. This included Graves’ disease and autoimmune hypo-/hyperthyroidism and was most common 3 to 4 years after initiating the drug. About 2% of patients who received alemtuzumab in the clinical trials developed an autoimmune platelet disorder (immune thrombocytopenic purpura) that causes easy bruising, spontaneous bleeding, and very low platelet counts (cells involved with clotting). Three tenths of a percent (0.3%) of the patients receiving alemtuzumab for MS developed a serious autoimmune kidney disease.
that can lead to kidney failure and dialysis if not detected and treated rapidly. Much of the autoimmunity with alemtuzumab occurs years after starting the drug. A recent review (Tuohy OJ et al 2014) of long-term safety in patients treated with alemtuzumab at Cambridge, England, reported secondary autoimmunity in 41/86 subjects (47%) and included some individuals treated with three or more cycles.

Several cases of cancer were identified in patients who received alemtuzumab, including three cases of thyroid cancer, four cases of melanoma, and several cases of lymphoma. Although these numbers are low, it is felt that alemtuzumab may increase the longer-term risk of malignancy.

Pneumonitis occurred in 6 of 1217 (0.5%) alemtuzumab-treated subjects, including hypersensitivity pneumonitis and pneumonitis with fibrosis.

Has the FDA included any black box warnings about this medication?

The following black box warnings are included in the prescribing information:

1. Lemtrada causes serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and antiglomerular basement membrane disease. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals for 48 months after the last dose of Lemtrada.

2. Lemtrada causes serious and life-threatening infusion reactions. Lemtrada must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for 2 hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2-hour monitoring period.

3. Lemtrada may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams.

4. Because of the risk of autoimmunity, infusion reactions, and malignancies, Lemtrada is available only through restricted distribution under a Risk Evaluation Mitigation Strategy (REMS) program.

What training is recommended or required for clinicians or patients before initiating this treatment?

Providers, health care facilities, pharmacies, and patients receiving alemtuzumab must all be registered in an FDA-mandated REMS program that includes education provided by the manufacturer of the drug. See below.
What is the pregnancy rating for this medication, and what is known about possible

carcinogenesis, mutagenesis, and impairment of fertility?

Alemtuzumab is pregnancy class C. Animal studies with alemtuzumab do not suggest
teratogenicity but suggest an increased rate of fetal death. Autoantibodies may cross
the placenta, resulting in fetal and neonatal adverse effects. Women of childbearing
potential receiving alemtuzumab are advised to use effective contraception while
receiving the drug and for 4 months following the course of treatment. Alemtuzumab
has been detected in the milk of lactating mice. It is not known if alemtuzumab is
excreted in human milk.

Does this medication interact or interfere with oral contraceptives?

Alemtuzumab is not known to interact with or interfere with oral contraceptives. The
recommendation from the manufacturer’s drug label is that two forms of birth control be
used during treatment to prevent pregnancy.

Has the FDA required a safety-monitoring program?

The FDA has mandated a REMS program to mitigate the risks of autoimmune
conditions, infusion reactions, and malignancies associated with alemtuzumab as part of
the approval to help ensure informed decisions about safe use of alemtuzumab:

• Informing patients about the serious risks of autoimmune conditions, infusion
  reactions, and malignancies associated with alemtuzumab and the need for baseline
  and periodic monitoring.
• Informing health care providers about the serious risks of autoimmune conditions,
  infusion reactions, and malignancies associated with alemtuzumab and the need to
  counsel patients and the need for baseline and periodic monitoring.

The REMS program will ensure safe use by:

• Ensuring that only certified prescribers prescribe alemtuzumab.
• Ensuring that alemtuzumab is dispensed only in approved health care settings by
certified pharmacies and certified infusion sites that have on-site access to equipment
and personnel trained to manage infusion reactions.
• Ensuring that only enrolled and authorized patients receive alemtuzumab.
• Ensuring that certified prescribers submit documentation of periodic monitoring
  of patients who receive alemtuzumab to identify autoimmune conditions and
  malignancies.
The REMS program includes a communications plan that includes the following:

- The manufacturer will send out a letter to health care providers within 60 days of approval, and then again yearly for 3 years, which will address the risks of alemtuzumab treatment and provide details of the REMS program.

- The manufacturer will ensure that the website www.lemtrada.com will be available and will contain information on the REMS program.

Lemtrada can be administered only by certified programs:

- **Prescribers** must be enrolled in the Lemtrada REMS Program to be able to prescribe Lemtrada.

- **Health care facilities and pharmacies** must be enrolled in the Lemtrada REMS Program to be able to dispense and/or administer Lemtrada.

- **Patients** must be enrolled and authorized in the Lemtrada REMS Program in order to receive Lemtrada.

In order to be certified to administer Lemtrada, a provider must:

- Review the prescribing information for the drug

- Review the REMS program by completing and signing the REMS prescriber enrollment form and submitting to the REMS program.

- Agree to:
  - Inform patients of the risks associated with the need for periodic monitoring and providing each patient with the patient guide and a safety information card.
  - Submit a REMS enrollment form for each patient, with a copy to the patient and to the patient’s medical record.
  - Submit a REMS order form for each prescription to the REMS program.
  - Perform required monitoring.
  - Submit the REMS patient authorization and baseline lab form to the REMS program within 30 days prior to the first infusion date.
  - Submit to the REMS program the REMS patient status form 6 months after the first infusion and every 6 months thereafter until 48 months after the completion of the last infusion.
  - Report any adverse events to the manufacturer.
  - Notify the manufacturer if the patient is no longer under the care of the original prescribing provider.
What kind of safety monitoring is recommended (including prescreening, routine checkups, and laboratory tests)?

- HPV (human papillomavirus) screening is recommended annually.
- Complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts should be obtained prior to initiation of treatment and at monthly intervals until 48 months after the last infusion.
- If an individual has not been immunized for varicella zoster virus, antibody testing should be performed (and vaccination performed if appropriate) at least 6 weeks prior to initiating therapy.
- Thyroid function tests should be obtained prior to the initiation of treatment and every 3 months until 48 months after the last infusion. Monitoring may need to continue past 48 months based on clinical findings of autoimmune conditions in postmarketing studies.
- Skin examination for melanoma should be performed prior to treatment and yearly thereafter.
- This medication can be administered only in certified health care settings that have on-site access to equipment and personnel trained to manage infusion reactions, including anaphylaxis and cardiac and respiratory emergencies.
- Patients should be advised to read the FDA-approved patient labeling (Medication Guide) and instructed to report promptly any symptoms that may be indicative of serious side effects or complications of this medication.

Are there any recommended limits on treatment duration with this medication?

The recommended dosage of alemtuzumab is 12 mg/day administered by intravenous infusion for 5 consecutive days, followed by three consecutive daily infusions 1 year later. There are no known limits on how long this treatment can be continued.

What happens following termination of treatment with this medication?

The effect of treatment on MS disease activity persists long-term: preliminary data suggest that over 80% of subjects who remained in the CARE-MS I and CARE-MS II extension study did not require further doses of alemtuzumab at 3 years. Preliminary data also suggest that the risk of autoimmune side effects from treatment with alemtuzumab appears to be highest between 3 and 4 years after treatment.
What treatment options are available for patients who have been treated with alemtuzumab?

Alemtuzumab treatment is associated with increased rates of certain viral infections and possibly some cancers. How long those increased risks persist after treatment is discontinued and whether the effects are additive with subsequent treatments is not known. Because it is not known whether risks are additive, providers should use caution when switching MS patients who have been treated with alemtuzumab to other immunosuppressive treatments or medications such as natalizumab and dimethyl fumarate that have been associated with progressive multifocal leukoencephalopathy.

What is the washout period?

The effects of treatment are thought to persist for at least 1 to 2 years after the last dose.

How can the provider identify a suboptimal treatment response?

Persistent evidence of inflammatory disease activity (clinical relapses and/or new and/or gadolinium-enhancing lesions on MRI of brain or spinal cord) could indicate a suboptimal response. Because alemtuzumab is not a cure for MS, clinical judgment is required to determine whether the response is suboptimal.

Is the manufacturer/distributor offering any financial assistance program for patients?

Genzyme MS support program: (1-855-MSOne2One; 1-855-676-6326); www.genzyme.com.

Copayments for Lemtrada are paid by the sponsor for patients who have inadequate insurance coverage and who have qualifying income levels. Appropriate patients may apply for free medication. The sponsor also covers all costs associated with monitoring for those who participate in the Centralized Lab Program offered by Genzyme.

Are there any special considerations with this medication?

Because of potential serious and/or life-threatening short- and long-term side effects of treatment, the use of alemtuzumab is restricted to prescribers certified under the FDA mandated REMS program, to distribution sources also certified under the REMS program, and to infusion centers trained under the same mandate.
COMMENTARY BY TEMPLATE AUTHORS
The full REMS program is available on the FDA website, www.FDA.gov/Alemtuzumab.

WEB LINKS PROVIDED IN THIS DOCUMENT
FDA prescribing information: http://products.sanofi.us/Lemtrada/Lemtrada.pdf

Genzyme: www.genzyme.com


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FOR COMPLETE DISCLOSURES AND OTHER INFORMATION:
Please visit our website at http://www.ms-coalition.org/emergingtherapies or email us at emergingtherapies@ms-coalition.org.

For additional information, healthcare professionals are invited to email the National MS Society’s Professional Resource Center at healthprof_info@nmss.org.
What is the medication?

**Generic:** Dimethyl Fumarate [formerly called BG-12]

**Brand name:** Tecfidera®

Oral medication (taken by mouth) approved by the US Food and Drug Administration (FDA) to treat relapsing multiple sclerosis (MS).

Has the FDA approved the medication?

**Yes** – on March 27, 2013, the FDA approved dimethyl fumarate.

If so, what is the recommended use in MS, and for whom is the medication recommended?

This medication is approved to treat patients with relapsing forms of MS. Relapsing forms include relapsing-remitting MS, progressive-relapsing MS, and secondary-progressive MS in those people who continue to have relapses.

What studies did the FDA look at when deciding whether to approve this medication?

What were the results of these studies?

Two large (Phase III) clinical trials have been conducted and published in the *New England Journal of Medicine*, September 20, 2012:

  - **What was the design of the study?**
    Three groups of people took part in this two-year study: one group was given 240 mg of dimethyl fumarate twice daily, a second group was given 240 mg of this medication three times daily, and a third group took a placebo capsule (without active medication in it).
  - **What questions was the study trying to answer?**
    This study was designed to answer several questions, including:
    - Do people taking dimethyl fumarate have fewer relapses (exacerbations or attacks) in a year than those taking the placebo?
    - Do people taking dimethyl fumarate have fewer lesions (spots) on MRI (magnetic resonance imaging) scans than people taking placebo?
    - Do people taking dimethyl fumarate experience less progression of disability than people taking placebo? (“Progression of disability” refers to a reduction in one's ability, usually in terms of mobility.)
Did the group taking dimethyl fumarate two times daily have different results or side effects than the group taking dimethyl fumarate three times daily?

- What were the results of the study?
  - People taking dimethyl fumarate at either the two-times-daily or three-times-daily dose had significantly fewer relapses than those taking placebo.
  - Progression of disability was reduced in people taking dimethyl fumarate as compared with those people taking the placebo. This was the case for individuals taking the medication either two times a day or three times a day.
  - MRI indications of MS disease activity showed greater benefit in the people taking dimethyl fumarate than in those taking placebo.
  - Side effects were similar in both groups receiving dimethyl fumarate.

  - What was the design of the study?
    Four groups of people took part in this two-year study: one group was given 240 mg of dimethyl fumarate twice daily; a second group was given 240 mg of this medication three times daily; a third group took a placebo (a capsule without active medication in it); and a fourth group received Copaxone (glatiramer acetate). The participants in the Copaxone group were aware of the drug they were taking, but the rater who measured the results was “blinded” and did not know which treatment these individuals were receiving.

    A Copaxone-treated group was included in this trial as a “reference comparator” (comparison group). However, the study was not designed to compare the effectiveness of dimethyl fumarate with the effectiveness of Copaxone.

  - What questions was the study trying to answer?
    This study was designed to answer several questions, including:
    - Do people taking dimethyl fumarate have fewer relapses (exacerbations or attacks) in a year than those taking the placebo?
    - Do people taking dimethyl fumarate have fewer lesions (spots) on MRI scans than people taking placebo?
    - Do people taking dimethyl fumarate experience less progression of disability than people taking placebo? (“Progression of disability” refers to a reduction in one’s ability, usually in terms of mobility.)
    - Did the group taking dimethyl fumarate twice daily have different results or side effects than the group taking dimethyl fumarate three times daily?
  - What were the results of the study?
    - People taking dimethyl fumarate at either the twice-daily or three-times-daily dose had significantly fewer relapses than those taking placebo.
Progression of disability did not differ significantly between the four groups.

- MRI measures of disease activity showed greater benefit in the people taking either dose of dimethyl fumarate as compared with those taking placebo.
- Side effects were similar in both groups receiving dimethyl fumarate.

**How does the medication work?**

It is not known how dimethyl fumarate exerts its effects in MS. Dimethyl fumarate is known to act on a pathway that may modulate the immune system and reduce inflammation. This pathway is also associated with the protection of cells from damage due to oxidative stress. This means that dimethyl fumarate may also help to protect the nerves from becoming damaged.

**How is this medication taken? What is the dosage, and how often is it taken?**

The dimethyl fumarate capsule is a timed-release medication that should be swallowed whole and not chewed, crushed, or opened and sprinkled on food. It is taken twice a day. The starting dose is 120 mg twice a day for seven days (14 capsules) and then is increased to the regular dose of 240 mg twice a day. A first-dose titration package contains the correct doses for the first month of use.

**Can this medication be used with other medications?**

- **Disease-Modifying Therapies**
  - Has this medication been tested in combination with other disease-modifying therapies?
    No published studies have evaluated the use of dimethyl fumarate in combination with other MS disease-modifying therapies. No specific concerns were identified for dimethyl fumarate and prior use of other MS disease-modifying therapies.

- **Other Medications**
  - Can dimethyl fumarate be taken with other medications a person is taking to manage MS symptoms or other medical problems?
    No specific concerns were identified in the pivotal trials (DEFINE and CONFIRM) regarding concurrent or prior use of other medications.

**What results can a person expect from this medication?**

- Dimethyl fumarate does not cure MS or make the symptoms of MS go away.
- Dimethyl fumarate was shown in clinical trials to reduce the rate of relapses and disease activity (as shown on MRI scans).
• No data are available yet to show whether dimethyl fumarate is effective in the long-term reduction of disability in MS.

What are the possible short-term side effects of this medication?

Dimethyl fumarate may cause flushing (which can create a sensation of heat or itching and a red blush on the skin) and gastrointestinal events (such as diarrhea, nausea, and upper abdominal pain). The incidence of these events during clinical trials was highest in the first month of treatment, decreasing thereafter. Taking the medication with food may reduce flushing. Dimethyl fumarate reduced blood lymphocyte (white blood cell) counts, but no increased risk of significant or severe infections was reported. Less common side effects included rash, itching, leakage of protein into the urine, and elevation of liver enzymes.

Most side effects were mild or moderate in severity. In the Phase III trials, gastroenteritis and gastritis were the only serious side effects (other than MS relapses) that occurred in two or more patients receiving dimethyl fumarate.

Can long-term health problems occur from use of this medication?

The long-term safety of dimethyl fumarate is unknown at this time. In the DEFINE and CONFIRM trials:

• Reduced lymphocyte (disease-fighting white cell) counts were seen during the first year. However, the number of infections during the trials was the same for all the groups.

• The number of malignancies (cancers) was low and similar between treated and placebo groups in the DEFINE trial; no malignancies were seen in the CONFIRM trial.

• Liver enzymes were higher in 6% of individuals treated with dimethyl fumarate as compared with 3% of the placebo group during the first six months of the DEFINE trial. No differences were seen in the CONFIRM trial, and no cases of liver failure were reported in either trial.

• Extra protein in the urine (proteinuria) was observed slightly more often in the groups receiving dimethyl fumarate as compared with the placebo group in the DEFINE study. No cases of kidney failure were reported in either trial.

Is training recommended or required for people who are starting this treatment?

No training is recommended or required.
What is known about how this medication affects reproduction (conception and pregnancy)?

Dimethyl fumarate is not approved for use during pregnancy. It has a pregnancy category C rating. This means that studies in laboratory animals revealed a reduced body weight in the mother and side effects related to survival, growth, and behavior in the developing fetus. Animal studies also revealed a delay in bone formation in the fetus.

A pregnancy registry has been established for women who accidentally become pregnant while taking dimethyl fumarate. This registry will track the outcomes of these pregnancies so that more can be learned about the possible effects of the medication on pregnancy. Women can enroll in the registry by calling 1-800-456-2255.

It is not known whether dimethyl fumarate passes into breast milk; caution is recommended before use by women who are breastfeeding.

Does this medication interact or interfere with oral contraceptives (birth control pills)?

No potential drug interactions with dimethyl fumarate have been identified.

Has the FDA recommended or required a safety-monitoring program?

The FDA has not required a safety-monitoring program for dimethyl fumarate.

Does the FDA recommend or require that people taking this medication be monitored for safety concerns?

The FDA recommends following safety monitoring procedures: Before starting treatment, the person should have had a recent (within six months) complete blood count (CBC) to make sure that her or his lymphocyte count is within normal limits. The CBC should be repeated annually and whenever the doctor feels it is necessary. The FDA also recommends that treatment with dimethyl fumarate should not be started in a person who has a serious infection of any kind. Treatment can be started as soon as the person has recovered from the infection.

How long can a person safely take this medication?

There are no recommended limits for treatment with dimethyl fumarate.
What happens if a person stops taking dimethyl fumarate?

As with discontinuing any disease-modifying therapy, MS activity may return following the discontinuation of dimethyl fumarate.

- Are there any risks associated with suddenly stopping the use of dimethyl fumarate?
  No rebound effect (sudden disease worsening) has been identified to date after stopping dimethyl fumarate. However, MS activity may occur during periods of no treatment.

- After stopping dimethyl fumarate, how long would a person have to wait before starting a different medication?
  There is no specific washout period recommended for dimethyl fumarate.

- What would a person do in the meantime?
  If waiting to begin treatment with another medication, a patient should work with his or her healthcare professional on a plan to manage symptoms and monitor for worsening of the MS.

How can a person tell if the medication is not working?

Dimethyl fumarate does not treat symptoms. This means that existing symptoms can continue to occur even if the medication is working. It is possible for relapses to occur while taking this medication and for new symptoms to appear. A person’s healthcare professional should evaluate any change in symptoms, relapse activity, and signs of disease progression during treatment. Certain tests, including an MRI, may be needed to determine whether the medication is working.

Is the manufacturer/distributor offering any financial assistance program for patients?

Biogen Idec offers comprehensive insurance and financial assistance programs, including a $10 copay program for individuals who are eligible. Contact MS SharedSolutions at 1-800-456-225 or at www.Tecfidera.com.

Are there any special considerations for this medication?

Dimethyl fumarate may decrease certain types of white blood cells that are important in the functioning of the immune system. A recent blood test (within 6 months) should be available before a person starts treatment in order to make sure that her or his lymphocyte count is within the normal range. Blood tests are also recommended annually and whenever the doctor feels they may be indicated.

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Bruce A. Cohen, MD, was a member of the independent neurologic evaluation committee which blindly reviewed relapse occurring in the dimethyl fumarate studies. Andrea Griesé has no disclosures. June Halper, MSN, APN-C, MSCN, FAAN, is a consultant and non-CME speaker for Acorda Therapeutics. Rosalind Kalb, PhD, has no disclosures. Ruth Whitham, MD, FAAN, has no disclosures.

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Please visit our website at http://www.ms-coalition.org/emergingtherapies or email us at emergingtherapies@ms-coalition.org.