National Multiple Sclerosis Society

Disease Modification in Multiple Sclerosis

Current as of January 2, 2013

Since 1993, the U.S. Food and Drug Administration (FDA) has approved several medications for use in multiple sclerosis. For the first time, we have the ability to reduce disease activity for many people with MS. These medications do not cure MS or provide relief from current symptoms—in fact, the effects on the disease may not be immediately apparent. However, each of these medications has been shown in phase III clinical trials to provide significant long-term benefit for people with relapsing forms of MS. Unfortunately, no medications have yet been approved for the treatment of primary-progressive MS.

And none of these medications are recommended for use by women who are pregnant or trying to become pregnant, or who are breastfeeding. Women should be encouraged to discuss all of their medications with their physician and/or nurse prior to trying to conceive.

Ongoing clinical trials are listed at www.nationalMSsociety.org/ClinicalTrials. Since new trials are announced periodically, and additional information becomes available as trials are completed, it is important to check these sites on a routine basis.

Five of the approved medications are delivered by injection; two are oral; and two are delivered by intravenous infusion. The injectable and oral options are considered first-line treatment options, meaning that the FDA does not require that any other medication be tried before prescribing one of these. The remaining two options are recommended for individuals who have not received sufficient benefit from one or more of the first-line options.

First-Line Medications

Five of the first-line medications are delivered by injection and two are taken orally. The five injectable therapies include two different formulations of interferon beta-1a (Avonex and Rebif), one formulation of interferon beta-1b that is marketed under two brand names (Betaseron and Extavia), and glatiramer acetate (Copaxone). Table 1 provides a side-by-side view of the first-line injectable medications. Table 2 provides a side-by-side view of the first-line oral medications.

TABLE 1: FIRST-LINE *INJECTABLE* DISEASE-MODIFYING MEDICATIONS – A SIDE-BY-SIDE VIEW

Betaseron® **Extavia®** interferon beta-1b	**Avonex®** interferon beta-1a	**Rebif®** interferon beta-1a	**Copaxone®** glatiramer acetate
MANUFACTURER/DISTRIBUTOR			
Bayer Healthcare Pharmaceuticals Inc. Novartis Pharmaceuticals	Biogen Idec	EMD Serono, Inc./Pfizer, Inc	Teva Neuroscience
APPROVAL			
Betaseron® -- 1993 US; 1995 Can – RRMS; 1995 Can – SPMS Extavia® -- 2009 US; 2009 Can	1996 US 1998 Can	1998 Can 2002 US	1996 US 1997 Can
FREQUENCY/ROUTE OF DELIVERY			
Every other day; subcutaneous injection	Weekly; intramuscular injection	Three times per week; subcutaneous injection	Daily; subcutaneous injection

TABLE 1: FIRST-LINE *INJECTABLE* DISEASE-MODIFYING MEDICATIONS – A SIDE-BY-SIDE VIEW – CONT'D

BRAND NAME AND GENERIC NAME			
Betaseron® **Extavia®** interferon beta-1b	**Avonex®** interferon beta-1a	**Rebif®** interferon beta-1a	**Copaxone®** glatiramer acetate
COMMON SIDE EFFECTS*			
Flu-like symptoms following injection, which lessen over time for many people; injection site reactions, about 5% of which need medical attention **Less common:** Depression, elevated liver enzymes, low white blood cell counts	Flu-like symptoms following injection, which lessen over time for many people **Less common:** Depression, mild anemia, elevated liver enzymes, liver toxicity	Flu-like symptoms following injection, which lessen over time for many people; injection site reactions **Less common:** Depression, elevated liver enzymes, low white blood cell counts	Injection site reactions **Less common:** A reaction immediately after injection that includes anxiety, chest tightness, shortness of breath, and flushing. This lasts 5-10 minutes and has no known long-term effects
PATIENT INFORMATION AND FINANCIAL SUPPORT PROGRAMS			
BETAPLUS 1-800-788-2467 *betaseron.com*	**MS Active Source** 1-800-456-2255 *avonex.com* *msactivesource.com*	**MS Lifelines** 1-877-44-REBIF (1-877-447-3243) *rebif.com* *mslifelines.com*	**Shared Solutions** 1-800-887-8100 *copaxone.com* *sharedsolutions.com* *mswatch.com*

Periodic liver function testing and complete blood count (CBC) are recommended for any patient taking an interferon medication.

TABLE 2: FIRST-LINE *ORAL* DISEASE-MODIFYING MEDICATIONS – A SIDE-BY-SIDE VIEW

BRAND NAME AND GENERIC NAME	
Gilenya™ fingolimod	**Aubagio®** teriflunomide
MANUFACTURER/DISTRIBUTOR	
Novartis Pharmaceuticals	Genzyme, a Sanofi company
Approval	
2010 US 2011 Can	2012 US
FREQUENCY/ROUTE OF DELIVERY	
Every day; capsule taken orally	Every day; pill taken orally
COMMON SIDE EFFECTS*	
Headache; flu, diarrhea, back pain, liver enzyme elevations, and cough **Less common:** Slowed heart rate following first dose, infections, swelling in the eye; See pages 12-13 for warnings.	Diarrhea, abnormal liver tests, nausea, flu, and hair thinning **Less common:** Lowered levels of white blood cells, which can increase the risk of infections; increase in blood pressure; severe liver damage; See pages xx-xx for warnings.
PATIENT INFORMATION AND FINANCIAL SUPPORT PROGRAMS	
Patient Support Program 1-877-408-4974	**MS One to One** 855-676-6326 MSOnetoOne.com

Interferon Beta Medications

Interferon beta, which is one of several kinds of interferon, was the first type of disease-modifying treatment to be approved for use in MS. Interferons are a group of proteins that are normally produced by cells in the immune system in response to viral infection and other conditions. They were named for their ability to interfere with viruses that are multiplying in the body. Interferon beta has a variety of effects on the immune system, including a reduction in those immune responses that attack the myelin and nerve fibers in MS. The four interferon beta medications that have been approved by the FDA are Betaseron (Bayer HealthCare Pharmaceuticals Inc.) and Extavia (Novartis Pharmaceuticals, Corp.), which are the identical formulation of interferon beta-1b distributed by two different companies; Avonex (Biogen Idec), and Rebif (Serono/Pfizer, Inc.), which are different formulations of interferon beta-1a. All are manufactured through the use of recombinant DNA technology.

All of the interferon medications should be used with caution by any person with a history of depression, liver or heart problems, epilepsy, thyroid problems or blood problems. Because of the potential of the interferon medications to affect the functioning of the liver and thyroid gland, and to alter the levels of white blood cells, red blood cells, and platelets in a person's system, blood tests are recommended at regular intervals.

- **interferon beta-1b (Betaseron; Extavia)**

  Approval by the U.S. Food and Drug Administration (FDA)

  Betaseron (Bayer HealthCare Pharmaceuticals Inc.) and Extavia (Novartis Pharmaceuticals, Corp.) are both approved to reduce the rate of relapses in people with relapsing forms of MS—which include relapsing-remitting MS, progressive-relapsing MS, and secondary-progressive MS in those people who continue to experience relapses. In addition, Betaseron and Extavia are approved for use by individuals who have experienced their first clinical episode and have MRI-detected brain lesions consistent with MS (referred to as clinically-isolated syndrome) but have not yet met the criteria for a definite MS.

  Interferon beta-1b is also approved in Canada under the name Betaferon.

  Clinical Outcomes

  Interferon beta-1b has been shown in clinical trials to reduce the frequency of relapses and the number of new lesions on MRI, and to delay the time to a second clinical episode (and therefore a confirmed diagnosis of MS) in those with clinically-isolated syndrome. Betaseron received FDA approval in 1993. Because Extavia is identical to Betaseron, the FDA did not require new clinical trials in order to approve Extavia in 2009.

  Route of Delivery and Side Effect Profile

Both Betaseron and Extavia are injected subcutaneously (under the skin) every other day, with the most frequent side effect being flu-like symptoms that gradually diminish over time. Some patients also experience injection site reactions consisting of pain, redness, inflammation, and occasionally tissue breakdown.

- **interferon beta-1a (Avonex)**

  Approval by the FDA

  Avonex (Biogen Idec) is approved by the FDA for the treatment of relapsing forms of MS, including relapsing-remitting MS, progressive-relapsing MS, and secondary-progressive MS in those individuals who are still experiencing relapses. In addition, Avonex is approved for people who have experienced their first clinical episode and have MRI-detected brain lesions consistent with MS (clinically-isolated syndrome) but have not yet met the criteria for a definite MS diagnosis.

  This medication is also approved in Canada.

  Clinical Outcomes

  Avonex has been shown in clinical trials to reduce the number of relapses and the number of new lesions on MRI, as well as to slow the progression of disability. Avonex has also been shown to delay the time to a second clinical episode (and therefore a confirmed diagnosis of MS) in people with a clinically-isolated syndrome.

  Route of Delivery and Side Effect Profile

  This medication is given by intramuscular injection once a week. The most common side effects of Avonex are flu-like symptoms that gradually diminish over time. Injection site reactions were rare.

- **interferon beta-1a (Rebif)**

  Approval by the FDA

  Rebif (Serono/Pfizer) is approved by the FDA for the treatment of relapsing forms of MS, including relapsing-remitting MS, progressive-relapsing MS, and secondary-progressive MS in those individuals who are still experiencing relapses.

  This medication is also approved in Canada.

Clinical Outcomes

Rebif has been shown to reduce the number of relapses as well as the number of new lesions on MRI. It has also been shown to delay the time to a second clinical episode (and therefore a confirmed diagnosis of MS) in people with a clinically-isolated syndrome, but the company has not applied to the FDA for approval of this use of the medication.

Route of Delivery and Side Effect Profile

This medication is given by subcutaneous injection three times per week, with the most frequent side effect being flu-like symptoms that gradually diminish over time. Some patients also experience injection site reactions consisting of pain, redness, inflammation, and occasionally tissue breakdown.

Glatiramer acetate

- **glatiramer acetate (Copaxone)**

Copaxone (Teva Neuroscience) is a synthetic compound made up of four amino acids (the building blocks of protein) that are found in myelin. This drug seems to block myelin-damaging T-cells through a mechanism that is not completely understood.

Approval by the FDA

Copaxone is approved by the FDA for the treatment of relapsing-remitting MS and for people who have experienced a first clinical episode and have MRI features consistent with MS.

This medication is also approved in Canada.

Clinical Outcomes

Copaxone has been shown to reduce the frequency of MS relapses, as well as the number and volume of brain lesions on MRI.

Route of Delivery and Side Effect Profile

This medication is delivered daily by subcutaneous injection. Injection site reactions, including pain, redness, inflammation, and occasionally tissue breakdown, are the most common side effect of Copaxone. On rare occasions, some people taking Copaxone also experienced a brief post-injection reaction involving shortness of breath, flushing, and chest tightening that subsided spontaneously after a few moments. This post-injection reaction is thought to have no lasting consequences.

Fingolimod

- **fingolimod (Gilenya)**

Gilenya (Novartis) is a new class of medication called a sphingosine 1-phosphate receptor modulator, which is thought to act by retaining certain white blood cells (lymphocytes) in the lymph nodes, thereby preventing those cells from crossing the blood-brain barrier into the central nervous system (CNS). Preventing the entry of these cells into the CNS reduces inflammatory damage to nerve cells.

Approval by the FDA

Gilenya was approved by the U.S. Food and Drug Administration (FDA) in 2010 for adults with relapsing forms of MS to reduce the frequency of clinical relapses and to delay the accumulation of physical disability.

This medication is also approved in Canada.

Clinical Outcomes

Gilenya has been shown to reduce relapses, the risk of disability progression, and brain lesion activity on MRI. In a one-year head-to-head trial with interferon beta-1a (Avonex), Gilenya was more effective in reducing relapses and disease activity.

Route of Delivery and Side Effect Profile

Gilenya is a capsule that is taken once daily. The most common side effects in the clinical trials of Gilenya were headache, influenza, diarrhea, back pain, abnormal liver tests, and cough. Gilenya may also cause a slowed heart rate, particularly after the first dose; an increased risk of infections; swelling of the macula in the eye.

Managing the Risks Associated with Gilenya

Because of the risk of a slowed heart rate after the first dose, the increased risk of infections, and swelling in the macula of the eye, the FDA recommends the following:

- Obtain a white blood cell count prior to treatment
- Test for antibodies to the varicella zoster virus (chicken pox) prior to treatment, and provide the vaccination if the person is antibody-negative
- Test the person's vision and repeat the testing after 3-4 months of treatment or any time the person reports vision changes.
- Monitor the patient's heart rate in the doctor's office for six hours after the initial dose.

In April, 2012, the FDA and the European Medicines Agency (EMA) revised the prescribing information for Gilenya, based on independent safety reviews initiated by the agencies after deaths were reported among patients taking Gilenya. The revised prescribing information defines who should avoid using this MS therapy based on pre-existing medical conditions, and alters the recommended testing and heart monitoring that occurs when the first dose is given.

In the U.S., the prescribing information update includes recommendations that:

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teriflunomide

- **teriflunomide (Aubagio)**

Aubagio (Genzyme, a Sanofi company) is a

Approval by the FDA

Aubagio was approved by the FDA for the treatment of patients with relapsing forms of MS in 2012. Two doses – 7mg and 14 mg – were approved

Clinical Outcomes

Both doses of Aubagio have been shown to reduce the rate of relapses and MRI measures of disease activity compared to placebo. The higher dose has also been shown to reduce disability progression.

Route of Delivery and Side Effect Profile

Aubagio is pill that is taken once daily. The most common side effects in the clinical trials of Aubagio were abnormal liver function, alopecia, diarrhea, influenza, nausea and paresthesias.

Managing the Risks Associated with Aubagio

Because of risks related to hepatotoxicity (black box warning), fetal death and malformations (black box warning), infections, skin reactions, blood pressure increase, and respiratory effects, the prescribing information recommends the following:

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  - *or*
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Additional Treatment Options

Table 3 provides a side-by-side view of the additional approved treatment options.

TABLE 3: ADDITIONAL APPROVED TREATMENT OPTIONS – A SIDE-BY-SIDE VIEW

BRAND NAME AND GENERIC NAME	
Tysabri® natalizumab	**Novantrone®** mitoxantrone
MANUFACTURER/DISTRIBUTOR	
Biogen Idec Elan Pharmaceuticals	Serono, Inc.
APPROVAL	
2006 US 2006 Can	2000 US
FREQUENCY/ROUTE OF DELIVERY	
IV infusion every four weeks in a registered infusion facility	Four times a year by IV infusion in a medical facility. Lifetime cumulative dose limit of approximately 8-12 doses over 2-3 years
COMMON SIDE EFFECTS*	
Headache, fatigue, urinary tract infections, depression, lower respiratory tract infections, joint pain, and chest discomfort. **Less common:** allergic or hypersensitivity reactions with two hours of infusion (dizziness, fever, rash, itching, nausea, flushing, low blood pressure, difficulty breathing, chest pain). See page XX for more information on side effects and risks associated with PML.	Blue-green urine 24 hours after administration, infections, bone marrow suppression (fatigue, bruising, low blood cell counts), nausea, hair thinning, bladder infections, mouth sores. Patients must be monitored for serious liver and heart damage. See page 19 for more information on side effects and risks.
PATIENT INFORMATION AND FINANCIAL SUPPORT PROGRAM	
1-800 456-2255 *Tysabri.com*	None at this time

Two additional treatment options are approved for use in MS.

Natalizumab

- **natalizumab (Tysabri)**

Tysabri (Biogen Idec/Elan Pharmaceuticals) is a laboratory-produced monoclonal antibody

that is designed to hamper the movement of potentially damaging immune cells from the bloodstream, across the blood-brain barrier, and into the brain and spinal cord. The drug inhibits this movement by attaching to alpha 4-integrin, a protein on the surface of immune T-cells that normally enables them to adhere to and pass through the blood-brain barrier. Because of this mode of action, Tysabri is called a selective adhesion molecule inhibitor (or "SAM").

Approval by the FDA

Tysabri is approved for all relapsing forms of MS. However, because of the risks associated with Tysabri, the FDA has recommended that it only be used by someone who has not received sufficient benefit from the first-line, injectable medications or has been unable to tolerate their side effects. The FDA further recommends that Tysabri should not to be used in combination with any of the injectable medications.

This medication is also approved in Canada.

Clinical Outcomes

Tysabri has been shown to reduce the risk of progression of disability, the number of clinical relapses, and the development of new lesions on MRI.

Mode of Delivery and Side Effect Profile

Tysabri is delivered by monthly intravenous infusion at approved infusion centers. The most common side effects associated with the monthly infusions include headache, pain in the extremities, fatigue, urinary tract infections, lung infections, vaginitis, joint pain, depression, diarrhea, and pain in the stomach area. Tysabri also increases a person's risk for a rare brain infection called progressive multifocal leukoencephalopathy (PML), which usually results in death or severe disability. PML is caused by the common JC virus, which generally lies dormant in a person's body. PML most often occurs in people whose immune system is suppressed by disease (e.g., AIDS) or by medications (e.g., immunosuppressants used to treat cancer or to prevent organ transplant rejection), resulting in activation of the JC virus.

Managing the Risks Associated with PML

Because of the risk of PML, Tysabri is available only through a special distribution program called the TOUCH Prescribing Program. The medication can only be prescribed and delivered by physicians, infusion centers, and pharmacies that are registered with the program. And only those patients who are enrolled in the program, and meet all the conditions set by the program, can receive this medication. Prior to starting treatment with Tysabri, and before each infusion, people will be evaluated at the infusion center to ensure that they are still appropriate candidates for this medication.

In January, 2012, the FDA approved a change to the prescribing label for Tysabri, indicating that a laboratory test to detect antibodies to the JC virus can help determine a person's risk of

developing PML. Testing positive for the presence of antibodies indicates that a person has at some point been infected by or exposed to the virus, which puts that person at higher risk of developing PML. Previous findings have identified two additional risk factors – use of an immune-suppressing medication at any time and taking Tysabri for more than two years.

The revised label suggests that the risks and benefits of starting or continuing Tysabri should be carefully considered in patients who test positive for antibodies to the JC virus and have one or more additional risk factors. Those found to be antibody positive, have used Tysabri for less than two years, and have no prior use of immune-suppressing drugs are estimated to a have a risk of PML of less than 1/1000; those with all three known risk factors have an estimated risk of PML of 11/1000 (Fox & Rudick, 2012).

A person who tests negative for anti-JC virus antibodies is still at risk for the development of PML for two very important reasons. First, she or he can be infected by the JC virus at any time without knowing it. Second, the laboratory test to detect antibodies to the JC virus will produce a false negative result about three percent of the time. Therefore, testing should be considered prior to starting treatment with Tysabri, as well as periodically while a person is on treatment. The availability of the laboratory test will help people with MS and their physicians to weigh risks and benefits of therapy.

Mitoxantrone

- **mitoxantrone (Novantrone)**

Novantrone (Serono) is a potent treatment that suppresses the immune system and has previously been used to treat one type of leukemia. It has also been used to treat pain associated with certain forms of prostate cancer. Novantrone acts by slowing the division of cells and altering other immune cells and substances.

Approval by the FDA

Novantrone is approved by the FDA to reduce neurologic disability and/or the frequency of clinical relapses in patients with secondary-progressive MS (with or without relapses), progressive-relapsing MS, or worsening relapsing-remitting MS. It is not approved for use in primary-progressive MS, nor is it commonly used as an initial treatment.

This medication has not been approved by Health Canada for the treatment of MS but can be used at the discretion of the physician for people with worsening relapsing-remitting or secondary-progressive MS.

Clinical Outcomes

Novantrone has been shown to slow progression of disability, reduce frequency of relapses, and reduce accumulation of new brain lesions as shown on MRI.

Mode of Delivery and Side Effects Profile

Novantrone is administered via intravenous (into the vein) infusion, once every three months. The short-term side effects, including nausea, hair loss, urinary tract infections, and menstrual disorders, are manageable and reasonably well tolerated. Novantrone also increases a person's risk of heart damage and secondary acute myelogenous leukemia (AML). The risk of AML is higher for those people who have previously been treated with certain types of chemotherapy drugs.

Managing the Risks Associated with Novantrone

The accumulated Class III and IV evidence since Novantrone was approved for use in MS suggests an increased incidence of systolic dysfunction and therapy-related acute leukemia (TRAL) with this medication. Systolic dysfunction occurs in approximately 12% of patients with MS treated with Novantrone, congestive heart failure occurs in approximately 0.4%, and leukemia occurs in approximately 0.8% (Marriott et al., 2010).

- Because of its potential long-term impact on cardiac function, the FDA cautions that the drug should only be used in those with normal heart function, and that cardiac monitoring should continue for the duration of the treatment and after treatment has been completed. Prior to the start of treatment, a person should be carefully evaluated (by examination and medical history) for signs and symptoms of heart disease.
    - Baseline evaluation of left ventricular ejection fraction (LVEF); patients with LVEF lower than 50% should not be given Novantrone.
    - Repeat LVEF testing prior to each dose of Novantrone; any person whose LVEF changes significantly or drops below 50% should have no further Novantrone treatments.
    - Annual LVEF testing following termination of treatment with Novantrone

- The factors that are known to increase a person's risk for cardiotoxicity with Novantrone are:
    - Current or prior history of heart disease
    - Simultaneous use of other medications that can damage the heart
    - Previous therapy with certain kinds of chemotherapies (anthracyclines or anthracenediones)

- Secondary acute myelogenous leukemia (AML), a type of cancer, has been reported in MS patients and cancer patients treated with Novantrone. In one group of MS patients treated with Novantrone, two out of 802 patients (.25%) developed AML. The risk of leukemia following treatment with Novantrone is increased for patients who have been treated with other types of chemotherapies called anthracyclines. Because post-marketing data collection is not controlled in any way, it is not possible to determine the exact risk for a person with MS of developing AML following treatment with Novantrone.

Other Treatments for Progressive Disease

To access information about disease modifying therapies for your patients, go to

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