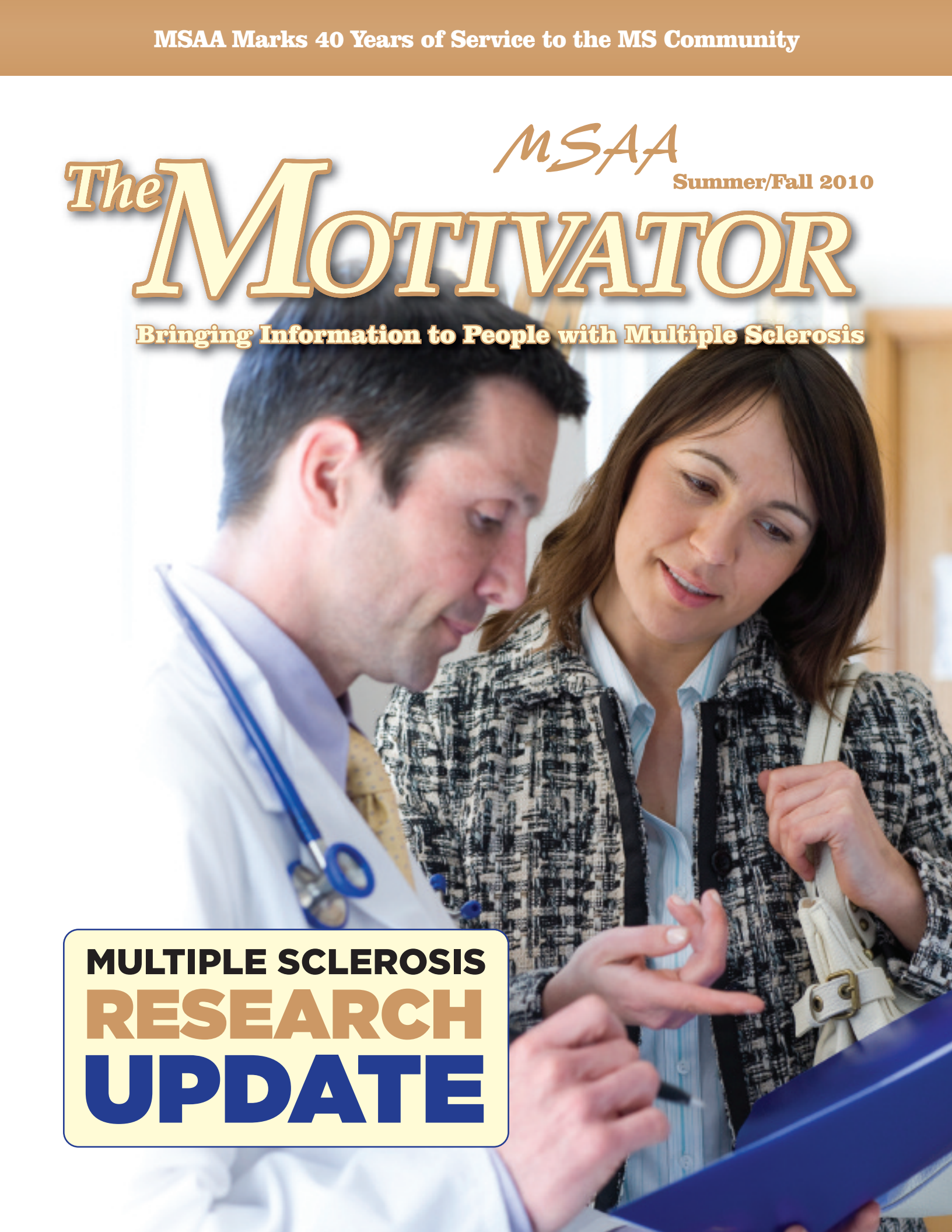
MSAA Marks 40 Years of Service to the MS Community

MSAA
Summer/Fall 2010

The MOTIVATOR

Bringing Information to People with Multiple Sclerosis



MULTIPLE SCLEROSIS RESEARCH UPDATE

MSAA™
MULTIPLE SCLEROSIS ASSOCIATION OF AMERICA

provides follow-up **Cranial MRIs for MS patients** to help track disease progression

The MRI Institute Program

is supported by a charitable contribution from EMD Serono, Inc. and Pfizer Inc

- This program covers the cost of Cranial MRIs for financially challenged MS patients who are uninsured
- MS patients must meet income eligibility guidelines and can only receive an MSAA-funded MRI every two years

To learn more or to download the **MRI Institute** application, visit **www.msassociation.org,** or call **(800) 532-7667, ext 120.**

The MOTIVATOR

Published by the Multiple Sclerosis Association of America

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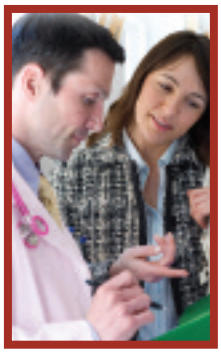
The Motivator's purpose is to inform and educate those with MS and their families. MSAA does not endorse or recommend any specific products, services, therapies, or activities mentioned in articles or advertisements that appear in *The Motivator.* MSAA, its staff, and those affiliated with the writing of this publication cannot be held responsible for any unintentional errors.

America's Charities MEMBER

2008 National Health Information Awards Winner

2008 APEX Publication Excellence

A portion of this magazine has been printed on recycled paper using soy-based ink.



COVER STORY

Multiple Sclerosis Research Update

A comprehensive overview of the eight FDA-approved disease-modifying therapies used to slow MS activity (including the newly approved oral therapy, Gilenya), and initial findings on many of the experimental treatments in development for the treatment of MS.

DEPARTMENTS

Please note: due to space limitations, our **Ask the Doctor** column (by MSAA's Chief Medical Officer Dr. Jack Burks) could not be included in this issue. However, we have posted this column on our website at **www.msassociation.org/publications/fall10/ask.asp**. Individuals without internet access may call MSAA at (800) 532-7667 to request a printed copy.

MSAA™ Multiple Sclerosis Association of America

The Multiple Sclerosis Association of America's mission is to enrich the quality of life for everyone affected by multiple sclerosis.

Up Front

By Douglas G. Franklin
MSAA President and CEO

Douglas G. Franklin

In this edition of *The Motivator*, our annual Research Update focuses on the FDA-approved and experimental therapies for MS. Much of the study data comes from two medical conferences that are held each spring: the American Academy of Neurology (AAN) Annual Meeting and the Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting. As always, MSAA was an active participant in these conferences and we are pleased to be able to share this information with you.

I am also pleased to announce that MSAA is marking its 40th year of service to the MS community. With humble beginnings as a grassroots organization serving the Philadelphia area, MSAA has grown into a national organization with six regional offices, serving more than 50,000 people each year. Today, MSAA continues to grow as a national leader in the MS community. In addition to our many programs and services that we provide, we are also one of the founding members of the MS Coalition, an affiliation of independent MS organizations dedicated to the enhancement of the quality of life for all those affected by MS.

Today, MSAA continues to grow as a national leader in the MS community.

We continue to increase our educational outreach through our regional offices to provide programming that is informative, objective and balanced. We are expanding our online presence with an updated website as well as the use of on-demand videos, webcasts and social networks. Over 300,000 people visited our website last year and more than 27,000 logged on to view one of our 28 educational videos. As we continue to move forward, it is my hope that with today's innovations in technology we will be able to serve more people in more places than ever before.

In closing, I want to thank all of our donors who have made this growth possible. Your support has been so important in helping us to reach such a large number of people – and it is proof positive of how much we can enrich the lives of everyone affected by MS everyday. ◆

Doug Franklin joined MSAA as President & CEO in 1999. He has a distinguished career in nonprofit leadership and is a former national trainer in strategic planning for the Peter Drucker Foundation. A published international expert in social marketing and corporate social investment, he is a graduate of four universities. He currently serves on the National Board of the Key Philanthropic Organizations Committee of the American Society of Association Executives; on the Executive Committee of Health First – America's Charities Board in Washington, DC; and as President of the Multiple Sclerosis Coalition.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/Safety/MedWatch, or call 1-800-FDA-1088.

TEVA NEUROSCIENCE®

COPAXONE®
(glatiramer acetate injection)

MULTIPLE SCLEROSIS RESEARCH UPDATE

By Diana M. Schneider, PhD and Jack Burks, MD • Edited by Susan Wells Courtney

Based on the positive response to the "MS Research Updates" published from 2007 through 2009 in *The Motivator*, this year's article incorporates new information about the eight approved disease-modifying therapies (DMTs), as well as numerous experimental drugs currently under investigation for the treatment of MS. Highlights and recent study results are provided for each drug. This is not a complete list and not all information is included. Initial findings should be considered as preliminary, as additional studies and/or evaluations may be needed.

This information is based on a wide range of sources, including the extensive journal literature on MS and its management, a review of ongoing clinical trials, and papers presented at major national and international conferences. These include annual conferences of the American Academy of Neurology (AAN), the Consortium of Multiple Sclerosis Centers (CMSC), and the Americas and European Committees for Treatment and Research in Multiple Sclerosis (ACTRIMS and ECTRIMS).

This has been an especially active year both for new studies on existing drugs, with increasing data that help improve their usage, and for new and upcoming therapies. A great deal of excitement surrounds a sizable number of oral agents, which show promising results based on earlier Phase II studies. Five of these oral agents are now being tested in Phase III studies. The data from Phase III studies of two of these oral agents, Gilenya (fingolimod) and cladribine, were published in the January 20, 2010 online version of the *New England Journal of Medicine*. On September 21, 2010, while this issue of *The Motivator* was in production, the announcement was made that Gilenya (pronounced as "Jil-EN-ee-ah") was approved by the Food and Drug Administration (FDA). This is the first oral disease-modifying therapy available for the long-term treatment of MS. The approval of an oral DMT option is exciting news for members of the MS community.

Additionally, cladribine has been granted Fast Track approval and may be approved by the FDA in the first quarter of 2011. A third drug, oral laquinimod, has recently been granted Fast Track status as well. Oral teriflunomide and BG-12 (dimethyl fumerate)

Topics Covered in this Article

Trial Phases for Investigating Drugs and Treatments

A **Phase I** clinical trial tests for safety in humans, with typically less than 100 "healthy" volunteers. Investigators observe how the human body responds to the medication to determine safe doses and related side effects. Phase I trials are referred to as "open label" and "unblinded," because everyone – the patient, medical staff and investigators, knows the drug and dose that each participant is receiving. Phase I trials can take several months to one year to complete.

Phase II clinical trials, which look at safety and efficacy (effectiveness), typically run for several months to two years. In this phase, approximately 100 to 300 people with the disorder (in this case, MS) are given either the active drug or a placebo (a medication that looks the same as the drug being tested but has no active ingredients). Phase II studies are often "double-blinded," meaning that the participants, medical staff and investigators are not told who is receiving the drug and who is receiving the placebo. These studies are also "randomized," so that participants are assigned to treatment groups (or "treatment arms") based on chance.

Roughly one-third of experimental medications for MS reach the **Phase III** clinical trial level. These trials can take several years to complete and involve 1,000 to 3,000 participants at many different medical locations. These studies are randomized, placebo-controlled, and double-blinded. They are designed to provide more information on a drug's safety and efficacy, as well as additional benefits, side effects, and adverse reactions. Upon completion, a data analysis is performed. If the results are favorable, an application for approval is submitted to the Food and Drug Administration (FDA), whose panel reviews the results and recommends approval if it finds the treatment to be beneficial and safe.

Phase IV clinical trials are conducted after a drug has been approved. Participants are enrolled to further monitor safety and side effects, while evaluating long-term efficacy.

are also in phase III studies with the hopes of filing for FDA approval in the near future. All of these drugs are described in detail in the sections to follow.

A brief overview of MS terms and clinical trials is on page 38. For an overview of the immune system in MS and how the disease-modifying therapies are thought to interrupt this process, please refer to the cover story from the Winter/Spring 2010 issue of *The Motivator* titled, "MS Process and Targets for Treatment." This may be found online at **www.msassociation.org/publications/winter10/cover.story.asp**

Please note that this article does not include medications for managing the symptoms of MS. Treatments for symptom management are the subject of an article in the Winter/Spring 2009 issue of *The Motivator*. This may be found online at **www.msassociation.org/publications/winter09/cover.story.asp**

For those without internet access, please call MSAA at **(800) 532-7667** to request a printed copy of any of the articles mentioned above.

Editor's note: MSAA does not endorse or recommend any specific products or therapies. Readers are advised to consult their physician before making any changes to their medication, diet, exercise, or other treatment regimen.

FDA-APPROVED MEDICATIONS

Avonex® *(interferon beta-1a)*

Parent company: *Biogen Idec*

Taken via weekly intramuscular injections; dosage is 30 mcg (micrograms).

Avonex was approved by the FDA in 1996 for relapsing MS and more recently for individuals with clinically isolated syndrome (CIS). CIS is defined as a single attack (or the appearance of one or more symptoms characteristic of MS) with a very high risk of developing MS, when no other diseases or causes for symptoms are apparent.

Avonex has been shown to reduce the number of relapses and lesions on magnetic resonance imaging (MRI), and slow the progression of physical disability. The drug has been shown to be both safe and effective.

Interferons appear to reduce inflammation by modulating a favorable balance between cells that increase inflammation and cells that decrease it.

The most recent ASSURANCE study includes 15-year data. It is evaluating the longer-term impact on the development of disability of early versus delayed initiation of therapy in relapsing-remitting MS (RRMS). Of the 172 participants who completed the original study, about half are still using Avonex, and significantly fewer of these individuals have reached an EDSS disability status of 6.0 or greater versus those who did not continue treatment. ("EDSS" refers to the Kurtzke Expanded Disability Status Scale, which measures disability in whole and half numbers from 1 to 10.)

Results suggest that ongoing disease activity (as shown on repeat MRI scans) while on therapy, may be a marker of suboptimal treatment response. The study is attempting to identify factors that predict a long-term positive response. For example, EDSS progression over the first two years appears to be a meaningful predictor of a poorer long-term outcome, even for those remaining on Avonex.

In a recent development, a Phase III clinical trial (ADVANCE) is enrolling patients with RRMS to determine the safety and efficacy of BIIB017, a "PEGylated" version of Avonex, as compared to placebo. Pegylation is a chemical modification of the interferon beta-1a molecule that allows it to be given subcutaneously (under the skin) every two or four weeks, in contrast to the current once-a-week intramuscular injection. The goal is to reduce the number of injections and the need for deep injections, while maintaining the positive effect of the drug. Outcome measures will include reductions in relapse rate, new brain lesions, and disability progression, as well as improvements in quality of life.

Combination and Comparative studies:
The ongoing three-year, Phase III CombiRx trial for RRMS is comparing three treatment arms: Avonex with Copaxone, Avonex alone, and Copaxone alone. No results are as yet available.

The ACT trial evaluated Avonex in combination with methotrexate (MTX), intravenous methylprednisolone (IVMP), or both, as compared to Avonex plus placebo. Methotrexate is an immunosuppressive

FDA-APPROVED MEDICATIONS

Avonex *(continued)*

drug and methylprednisolone is a steroid that decreases inflammation.

In a study of 313 individuals with RRMS, those in the IVMP/interferon group showed a 38-percent decrease in relapses over those who took the placebo. Additionally, brain lesions stayed the same size or shrank in the treated group, while brain lesions in the placebo/interferon group enlarged. Results after the first year, however, were not as significant. One of the investigators, Dr. Jeffrey Cohen, noted that this trial did not demonstrate a benefit to adding low-dose oral methotrexate or every other month IV methylprednisolone to interferon beta-1a (Avonex) in RRMS.

A Phase II study combined Avonex with atorvastatin in patients with CIS. The study's primary endpoint was the development of three new T2 lesions or one clinical exacerbation within 12 months. Although the primary endpoint was not met, the proportion of patients who did not develop new T2 lesions was 55.3 percent in the atorvastatin group versus 27.6 percent in the placebo group. Further study is needed.

Pregnancy outcomes from the Avonex Pregnancy Exposure Registry, which included a total of 262 pregnancies (193 live births, 28 spontaneous abortions, four induced abortions, one still birth, 30 pending outcome, and six lost to follow-up), did not show an increase in the rate of major/serious birth defects over the general population. A Swiss study had similar results, indicating that the frequency of a major congenital anomaly was similar to that in the general population in pregnancies carried to term.

A German study showed no increase in malignancy risk in patients with MS receiving interferon beta-1a.

Betaseron® *(interferon beta-1b)*

Parent company: *Bayer HealthCare Pharmaceuticals*

Administered by subcutaneous injection every other day; dose is 250 mcg.

Approved for relapsing forms of MS in 1993, and more recently, for individuals with CIS.

Betaseron reduces the number and severity of exacerbations (attacks) of MS. It also stabilizes the total lesion area as measured by MRI, compared to those without treatment.

Interferons appear to reduce inflammation by modulating a favorable balance between cells that increase inflammation and cells that decrease it.

The BENEFIT trial evaluated the impact of Betaseron on patients with CIS. The risk for developing clinically definite MS (CDMS) was reduced by approximately 50 percent at two years versus placebo-treated patients. The risk for confirmed progression of sustained disability was reduced by 40 percent at three years (but not at five years) in those receiving Betaseron from the onset of CIS, versus those people whose treatment was delayed. Positive cognitive effects were maintained at five years.

FDA-APPROVED MEDICATIONS

Betaseron *(continued)*

Follow-up data after 16 years from Betaseron's initial Phase III trial of RRMS show continued effectiveness and safety. The results suggest that early treatment was more effective when given early in the course of the disease.

In the BECOME study, new MRI techniques compared Betaseron to Copaxone in RRMS. The study found that enhancing lesions and clinical data were similar, but that there were fewer hypointense lesions ("black holes") in the Betaseron-treated patients.

The BEYOND study compared Betaseron versus double-dose Betaseron versus Copaxone in early RRMS patients. All were well tolerated, and dramatically and equally reduced relapses. The T2-lesion volume MRI data favored Betaseron. As a result of this study, double-dose Betaseron will not be pursued since it was no more effective than the standard dose of Betaseron.

The Phase IV BETAPATH study of 800 individuals and the related SEPLUS study of 70 patients are evaluating strategies to improve adherence to therapy. This includes the use of a personal digital assistant (PDA) and participation in the BetaPlus mentoring program.

A Phase IV telephone interview study began in September 2009 and was scheduled for completion in April 2010. In this study, 372 individuals who had participated in the original pivotal Betaseron study, at 20 years after treatment, were interviewed. The primary outcome measure is to determine mortality EDSS (those who reached 10 on the EDSS scale), cognition, resource use, rate of conversion from RRMS to secondary-progressive MS (SPMS), and employment history by length of exposure to Betaseron.

Preliminary data from the Betaseron Pregnancy Registry includes information on 69 women who became pregnant while exposed to Betaseron; there were 59 live births, eight spontaneous abortions, and two stillbirths. Among the live-born infants, birth defects were reported in three, a frequency consistent with that of the general population. These data do not suggest an increased risk for birth defects; however, caution is urged until the study is completed.

Extavia® *(interferon beta-1b)*

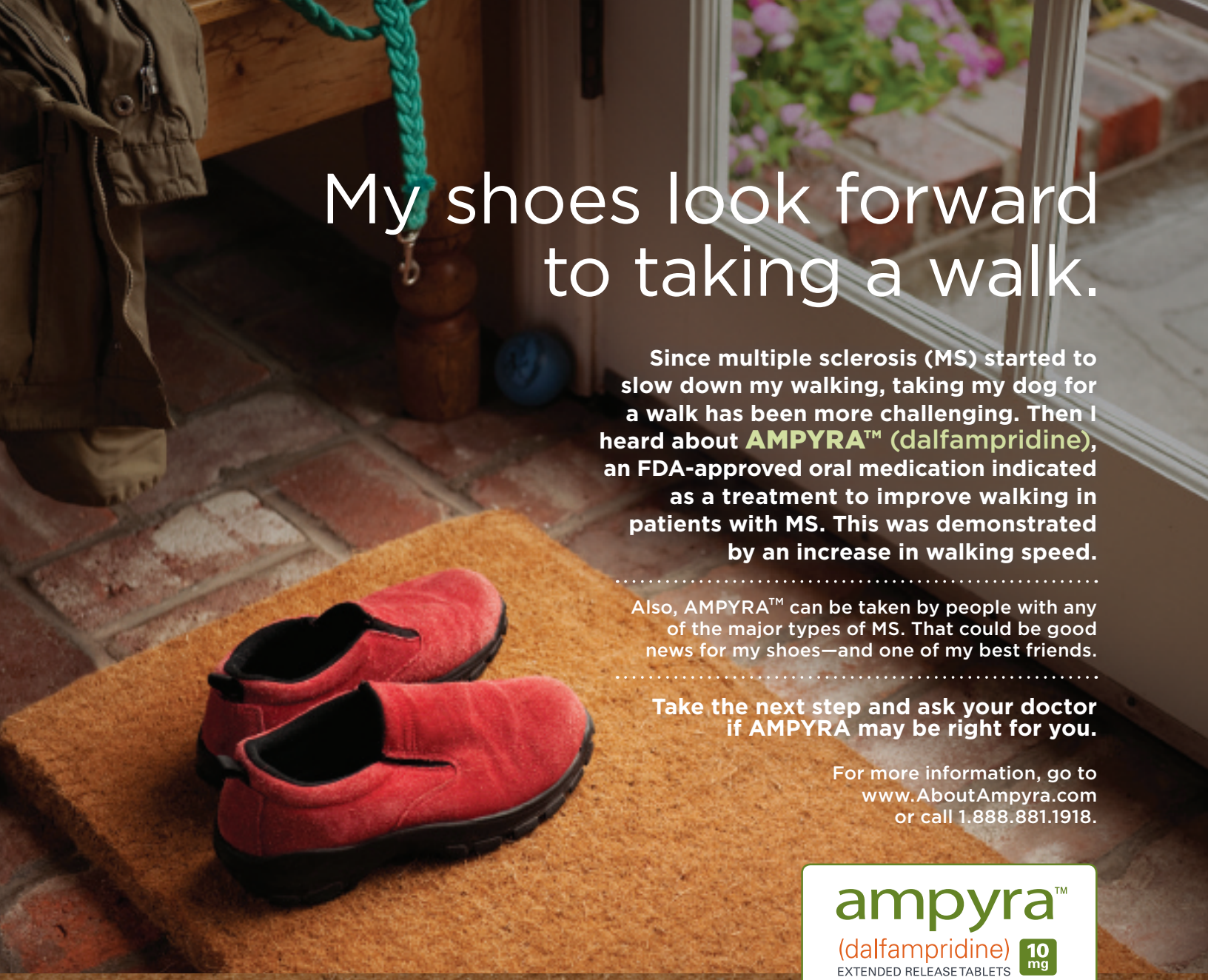
Parent company: *Novartis Pharmaceuticals Corp.*

Administered by subcutaneous injection every other day; dose is 250 mcg.

Approved for relapsing forms of MS and for individuals with CIS.

Extavia is an interferon beta-1b that is biologically identical to Betaseron and made in an identical process, but marketed by a different company. It was released in early 2010.

Extavia shares all prescribing, side effect, and safety information with Betaseron. The two pharmaceutical companies manage the patient support programs differently; prices and copayments also may vary. The latest information is available through the patient support programs at these two companies.



My shoes look forward to taking a walk.

Since multiple sclerosis (MS) started to slow down my walking, taking my dog for a walk has been more challenging. Then I heard about AMPYRA™ (dalfampridine), an FDA-approved oral medication indicated as a treatment to improve walking in patients with MS. This was demonstrated by an increase in walking speed.

Also, AMPYRA™ can be taken by people with any of the major types of MS. That could be good news for my shoes—and one of my best friends.

Take the next step and ask your doctor if AMPYRA may be right for you.

For more information, go to www.AboutAmpyra.com or call 1.888.881.1918.

ampyra™
(dalfampridine) 10 mg
EXTENDED RELEASE TABLETS

IMPORTANT SAFETY INFORMATION:

Talk to your doctor about AMPYRA to learn if it is safe for you. Do not take it if you've ever had a seizure or if you have certain types of kidney problems as this may increase your risk of seizure. Tell your doctor if you have kidney problems.

Never take more than one tablet of AMPYRA twice a day (about 12 hours apart). Don't take more than 2 tablets in a 24-hour period because it may increase the risk of seizures. If you miss a dose of AMPYRA don't make up the missed dose.

Do not take AMPYRA together with other aminopyridine medications, including compounded 4-aminopyridine (sometimes called 4-AP, fampridine).

AMPYRA may cause serious side effects, including kidney or bladder infections. The most common side effects are urinary tract infection, trouble sleeping (insomnia), dizziness, headache, nausea, weakness, back pain, and problems with balance. Tell your doctor if you have any of these side effects that bother you or do not go away.

For more information, please refer to the Medication Guide. This important safety information is not meant to replace discussions with your doctor. For more information call toll-free 1-888-881-1918.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

AMP166

ACORDA® THERAPEUTICS

MEDICATION GUIDE FOR AMPYRA™ (am-PEER-ah) (dalfampridine) Extended Release Tablets

Read this Medication Guide before you start taking AMPYRA.

Read this Medication Guide before you start taking AMPYRA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about AMPYRA?

AMPYRA can cause seizures.

- Your chance of having a seizure is higher if you take too much AMPYRA or if you have kidney problems.
- Do not take AMPYRA if you have ever had a seizure.
- Before taking AMPYRA tell your doctor if you have kidney problems.
- Take AMPYRA exactly as prescribed by your doctor. See "How do I take AMPYRA?"

Stop taking AMPYRA and call your doctor right away if you have a seizure while taking AMPYRA.

What is AMPYRA?

AMPYRA is a prescription medicine used to help improve walking in people with multiple sclerosis (MS). This was shown by an increase in walking speed.

It is not known if AMPYRA is safe or effective in children less than 18 years of age.

Who should not take AMPYRA?

Do not take AMPYRA if you:

- have ever had a seizure
- have certain types of kidney problems

What should I tell my doctor before taking AMPYRA?

Before you take AMPYRA, tell your doctor if you:

- have any other medical conditions
- are taking compounded 4-aminopyridine (fampridine, 4-AP)
- are pregnant or plan to become pregnant. It is not known if AMPYRA will harm your unborn baby. You and your doctor will decide if you should take AMPYRA while you are pregnant
- are breast-feeding or plan to breast-feed. It is not known if AMPYRA passes into your breast milk. You and your doctor should decide if you will take AMPYRA or breast-feed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Know the medicines you take.

Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take AMPYRA?

- Take AMPYRA exactly as your doctor tells you to take it. Do not change your dose of AMPYRA.
- Take one tablet of AMPYRA 2 times each day about 12 hours apart. Do not take more than 2 tablets of AMPYRA in a 24-hour period.
- Take AMPYRA tablets whole. Do not break, crush, chew or dissolve AMPYRA tablets before swallowing. If you cannot swallow AMPYRA tablets whole, tell your doctor.
- AMPYRA is released slowly over time. If the tablet is broken, the medicine may be released too fast. This can raise your chance of having a seizure.
- AMPYRA can be taken with or without food.
- If you miss a dose of AMPYRA, do not make up the missed dose. Do not take 2 doses at the same time. Take your next dose at your regular scheduled time.
- If you take too much AMPYRA, call your doctor or go to the nearest hospital emergency room right away.
- Do not take AMPYRA together with other aminopyridine medications, including compounded 4-AP (sometimes called 4-aminopyridine, fampridine)

What are the possible side effects of AMPYRA?

AMPYRA may cause serious side effects, including:

- Kidney or bladder infections

  See "What is the most important information I should know about AMPYRA?"

The most common side effects of AMPYRA include:

- urinary tract infection
- trouble sleeping (insomnia)
- dizziness
- headache
- nausea
- weakness
- back pain
- problems with balance
- multiple sclerosis relapse
- burning, tingling or itching of your skin
- irritation in your nose and throat
- constipation
- indigestion
- pain in your throat

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of AMPYRA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store AMPYRA?

- Store AMPYRA at 59°F to 86°F (15°C to 30°C).
- Safely throw away AMPYRA that is out of date or no longer needed.

Keep AMPYRA and all medicines out of the reach of children.

General Information about the safe and effective use of AMPYRA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AMPYRA for a condition for which it was not prescribed. Do not give AMPYRA to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about AMPYRA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about AMPYRA that is written for health professionals.

For more information, go to www.AMPYRA.com or call 1-800-367-5109.

What are the ingredients in AMPYRA?

Active ingredient: dalfampridine (previously called fampridine)
Inactive ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Distributed by: Acorda Therapeutics, Inc.
Hawthorne, NY 10532

Issued 01/2010

This Medication Guide has been approved by the U.S. Food and Drug Administration.

0510427AR-0

ACORDA®
THERAPEUTICS

FDA-APPROVED MEDICATIONS

Rebif® *(interferon beta-1a)*

Parent company: *EMD Serono, Inc. and Pfizer Inc*

Administered by subcutaneous injection three times weekly; dosage is 22 or 44 mcg. The 44 mcg dose appears significantly more effective than 22 mcg, and is the dose most often used in the United States.

Approved for relapsing types of MS.

Rebif reduces the frequency of relapses and slows the progression of disability. It also has been shown to reduce MRI lesion area and activity compared to placebo.

Interferons appear to reduce inflammation by modulating a favorable balance between cells that increase inflammation and cells that decrease it.

The Rebif new formulation (RNF) is not yet approved by the FDA, but it is designed to be better tolerated and to minimize the development of neutralizing antibodies that may decrease the response to treatment. The completed IMPROVE trial documented the efficacy of RNF in RRMS, as measured by the number of active lesions on MRI at 16 weeks. Again, this formulation is not yet available in the United States.

The ongoing STAR study has as its primary outcome measure the proportion of participants with injection-site reactions. Secondary measures include the occurrence of adverse events, the number and reason for missed injections, the proportion of relapse-free patients, and time to first relapse.

A once-weekly dose of Rebif previously demonstrated an effect on delaying CDMS after CIS. An ongoing study is looking at the use of Rebif 44 mcg for CIS to confirm its effectiveness in delaying the conversion to CDMS.

A 96-week trial of methylprednisolone as an add-on to Rebif is reported to significantly reduce the relapse rate in participants who showed clinical activity during interferon therapy. Half of the group received an MS treatment using interferon beta-1a plus 200 mg of oral methylprednisolone given in a "pulse therapy" fashion (200 mg on five consecutive days every four weeks), while the other half received interferon beta-1a plus a placebo treatment. The authors concluded that adding methylprednisolone led to a reduction in relapses. High dropout rate was a problem due to the side effects associated with steroids.

The Phase IV SKORE study is evaluating cognition and fatigue in people with RRMS treated with Rebif. Its primary outcome measure is the percentage of patients with stable or altered cognition status; secondary outcome measures are the proportion of relapse-free subjects and the proportion with defined EDSS changes. The study has 300 participants; it was initiated in June 2009 and is scheduled for completion in November 2013.

The ongoing Phase II RECYCLINE study combines Rebif with minocycline (an antibiotic that has immunomodulatory properties). The study, which has 320 participants, began in March 2006 and is estimated to be completed in February

FDA-APPROVED MEDICATIONS

Rebif *(continued)*

2012. The primary outcome measure is the time to first relapse; secondary outcome measures include the average number of relapses per subject, the number of new or enlarging lesions on T2-weighted MRI; brain atrophy; and time to confirmed progression in disability. No data have as yet been published.

The European COGIMUS study measured changes in depression, fatigue, quality of life, and social functioning in patients with RRMS treated with interferon beta-1a. It found that these parameters remained relatively stable over the three years of the study.

Copaxone® *(glatiramer acetate)*

Parent company: *Teva Neuroscience*

Given through daily subcutaneous injections; dosage is 20 mg.

Approved for RRMS.

Copaxone has been shown to significantly reduce the annual relapse rate in RRMS and reduce the risk of developing clinically definite MS (CDMS) at two years.

Copaxone is a synthetic polypeptide that mimics myelin basic protein, a key component of the myelin sheath that is damaged in MS. It appears to decrease immune system T cells that damage myelin, and may decrease inflammation by shifting the balance among T-cell subtypes as well as by affecting several interleukins. It also may induce lymphocytes to produce factors that enhance the survival of cells that produce myelin, and may have a neuroprotective action that prevents damage to axons.

Data is now available for 15 years of Copaxone treatment. Only one-third of patients who remain on Copaxone experience disease progression as defined by conversion to SPMS; 57 percent have experienced stable or improved EDSS scores; and 82 percent remain ambulatory without mobility aids. No long-term safety issues have occurred. This study will continue to 20 years.

The Phase III, 36-month PreCISe study showed that fewer patients with clinically isolated syndrome (CIS) developed CDMS in the treated group than in the placebo group. The conversion of CIS to CDMS was delayed. The time at which 30 percent of patients had converted to CDMS was 569 days in the interferon group and 252 in the placebo group. Additionally, the number of new T2-weighted MRI lesions and the increase in lesion burden were significantly lower in the treated group.

An Austrian study indicated that a switch from interferon treatment to Copaxone might be beneficial for individuals who discontinued interferon treatment because of a lack of effectiveness. However, those who switched from an interferon to Copaxone due to side effects showed no substantial change.

Preliminary evidence suggested that long-term maintenance treatment with

FDA-APPROVED MEDICATIONS

Copaxone *(continued)*

Copaxone following immunosuppressive therapy with Novantrone may be effective and well tolerated for individuals with rapidly progressive MS and may stabilize the disease. However, Novantrone use has decreased dramatically in the United States due to adverse effects. (Please see page 18 for more information on Novantrone.)

A Phase IV study of 60 patients with CIS or early RRMS will assess the effects of Copaxone on the condition of the optic nerve, using the noninvasive technique of optical coherence tomography as an alternative to MRI scanning for follow-up. The study began in September 2009 and is scheduled for completion in June 2012. A parallel Phase III study of 200 individuals with a first episode of optic neuritis will evaluate changes in the retina with Copaxone therapy.

Combination and Comparative studies:
The COMBI Rx trial is still ongoing, and is comparing the combination of Avonex plus Copaxone to Copaxone alone and Avonex alone. No data have as yet been reported.

A Phase II study found that Copaxone taken with oral minocycline reduced the number of new and active lesions. The two drugs were also reported to be safe and well tolerated when taken concurrently.

A Phase II trial to study the effect of combining Copaxone and estriol (a naturally-occurring estrogen hormone) in RRMS on relapse rate began in March 2007 and is scheduled for completion in September 2013. A total of 150 female participants will be enrolled, and the duration of active treatment is two years. The study will evaluate relapse rate, severity of relapses, and changes in the EDSS. If successful, this clinical trial could lay the groundwork for a larger, definitive trial that might lead to a new oral treatment option for women with MS.

A study of oral prednisone in 500 relapsing MS patients treated with Copaxone is ongoing. Its primary outcome will be changes in brain volume after three years.

Gilenya® *(fingolimod, FTY720)*

Parent company: *Novartis Pharmaceuticals Corp.*

Oral medication; 0.5 mg capsule taken once daily.

Approved for relapsing forms of multiple sclerosis (MS).

Gilenya (pronounced as "Jil-EN-ee-ah") is the first in a new class of immunomodulatory drugs, called S1P-receptor modulators. Gilenya is similar in structure to a naturally occurring component of cell surface receptors on white blood cells. It blocks potentially damaging T cells from leaving lymph nodes, lowering their number in the blood and tissues. It may reduce damage to the CNS and enhance the repair of damaged neurons. Animal data suggest that Gilenya may have neuroprotective effects.

In September 2010, the FDA approved this drug as a first-line treatment for relapsing

FDA-APPROVED MEDICATIONS

Gilenya *(continued)*

forms of MS. Gilenya is the first oral disease-modifying therapy available for the long-term treatment of MS.

The most commonly reported side effects with Gilenya include headache, flu, diarrhea, back pain, abnormal liver tests and cough. Women are strongly advised to use contraception to avoid pregnancy while taking Gilenya – and to continue contraception for two months following the discontinuation of the drug. The makers of Gilenya also strongly advise against breastfeeding.

Adverse events with Gilenya include: a reduction in heart rate (dose-related and transient); infrequent transient AV conduction block of the heart; a mild increase in blood pressure; macular edema (a condition that can affect vision, caused by swelling behind the eye); reversible elevation of liver enzymes; and a slight increase in lung infections (primarily bronchitis). Other infections, including Herpes infection, are also of concern.

A number of precautionary steps have been put in place to minimize risks and enable doctors to better evaluate and treat any possible adverse events. Within six months prior to starting Gilenya, patients should be given a baseline evaluation of any issues with the heart, lungs, liver, eyes and vision, as well as white blood cell count (which may indicate an existing infection). Present medications also need to be considered. Vitals (blood pressure, pulse, etc.) should be taken at baseline and periodically while on treatment.

Since the drug causes a reduction in circulating white blood cells, individuals considering Gilenya also need to indicate if they have had chicken pox or a chicken pox vaccination recently; if so, they may need to wait before starting the medication. Individuals who test negative for the chicken pox virus may need to be vaccinated and delay starting Gilenya. Patients will also need to avoid vaccinations with live viruses.

When beginning the drug, patients must be observed at a medical facility for the first six hours following the first dose. This is necessary as Gilenya may slow the heart rate, with the most significant drop usually occurring within the first six hours. While taking this drug, patients need to contact their doctor immediately if they experience any symptoms such as dizziness, tiredness, slow or irregular heartbeat, breathing difficulties, visual changes, or signs of an infection or liver problem.

A Risk Evaluation and Mitigation Strategy (REMS) has been approved to provide information to patients as well as healthcare professionals on how to use the drug safely, along with possible risks that may occur. Novartis will conduct a five-year observational safety study to further evaluate any adverse events. They have also organized a voluntary registry for women who become pregnant while taking or within two months after discontinuing Gilenya to document possible effects.

FDA-APPROVED MEDICATIONS

Gilenya *(continued)*

Study Information:
The FREEDOMS Phase III study of low-dose (0.5 mg) and high-dose (1.25 mg) Gilenya versus placebo is scheduled to end in March 2011. Outcome measures to date show the drug to be safe and well tolerated. Interim data show a 60-percent reduction in annualized relapse rate, a significant reduction in disability progression, a 74 to 82-percent reduction in the burden of disease as measured by MRI, and a reduction in whole-brain atrophy.

An extension study, FREEDOMS II, evaluated long-term safety, tolerability and efficacy; all 1,080 participants received Gilenya. Two deaths resulted from Herpes virus infection in the FREEDOMS trials; both of these individuals had received a higher dose than that submitted to the FDA. No deaths were reported in the lower-dose group, which used the same dose as approved by the FDA.

The TRANSFORMS Phase III trial was a 12-month study of the efficacy of two doses of Gilenya (0.5 mg and 1.25 mg) as

The New Oral Medications: Questions for Your Healthcare Provider

The new oral medications, including the recently approved drug Gilenya, have the advantage of not requiring injections or infusions, as with drugs approved prior to September 2010. Additionally, oral drugs might not be associated with some of the side effects of the earlier drugs, including flu-like reactions. But these new drugs are not without potential side effects and adverse events, which need to be discussed with your healthcare provider prior to making any treatment decisions.

If you are considering whether you should change to an oral medication, ask your doctor the following questions:

- Am I responding well to my current disease-modifying therapy?
- Do you have concerns about the effectiveness and side effects of my current medication? If so, what recommendations might you have, such as more testing, more frequent appointments, or a change in the management of side effects?
- Aside from taking a pill versus using an injection, what advantages do the oral therapies offer?
- How does the effectiveness, side effects and risks of the oral medication compare with my current medication?
- Has the FDA mandated any recommendations for monitoring safety with the oral drug?
- Would the oral medication interfere with any of the drugs I take for symptom management?
- What are the guidelines for pregnancy and reproduction with the oral medication?

All of the disease-modifying therapies for MS have different benefits and risks. Choosing a treatment is a very individualized decision, so your best plan of action is to develop a partnership with your doctor and to gather as much information as possible.

FDA-APPROVED MEDICATIONS

Gilenya *(continued)*

compared to weekly intramuscular injections of Avonex in individuals with RRMS. Its primary outcome measure was a reduction of relapse rate. Secondary measures included frequency of relapses, inflammatory disease activity as measured on MRI, and time to progression of disability.

In the TRANSFORMS trial, the annualized relapse rate was lower with Gilenya 0.5 mg (0.16) versus Avonex (0.33) at 12 months. The proportion of relapse-free patients was also higher with Gilenya. In summary, Gilenya was more effective in reducing relapse rate and relapse frequency, resulted in less deterioration in the ability to independently perform daily activities, was associated with a lower rate of brain atrophy, and showed a greater effect on reducing MRI measures of lesion activity.

Another new clinical trial began in April 2010. It has 1,850 participants, all of whom are receiving Gilenya. This trial is scheduled for completion in April 2011. The primary outcome measure is the safety and tolerability profile in patients with relapsing forms of MS. Secondary measures include the incidence of macular edema (swelling behind the eye) and any changes in heart rate or function as seen on an electrocardiogram. Secondary measures also include patient-reported outcomes based on surveys of health status and treatment satisfaction.

The 36-month INFORMS study in 940 individuals is the only trial now ongoing for primary-progressive MS (PPMS). It will evaluate the effect of Gilenya relative to placebo on delaying the time to sustained disability progression, as well as safety, tolerability and the effects on MRI parameters.

Tysabri® *(natalizumab)*

Parent company: *Biogen Idec and Elan Pharmaceuticals*

Administered via intravenous infusion every four weeks. Dose is 300 mg.

Approved for individuals with relapsing types of MS. This drug is generally recommended for patients who have not responded adequately, or who cannot tolerate, another treatment for MS.

At 18 months and up to 24 months of treatment with Tysabri, 87 percent of RRMS patients previously treated with other disease-modifying therapies showed stable or improved MRI scans. In this same group, disability scores as measured by EDSS were stable or improved in 59 percent of patients.

This laboratory-produced monoclonal antibody acts against a molecule involved in the activation and function of lymphocytes and their migration into the central nervous system (CNS). Recent data suggest that it may also enhance myelination and stabilize damage to the myelin sheath. Preliminary results suggest that the drug may actually produce an improvement in function.

Recent studies indicate that the drug increases the cumulative probability of achieving a sustained improvement in

FDA-APPROVED MEDICATIONS

Tysabri *(continued)*

disability in RRMS, and substantially reduced clinical and MRI activity after breakthrough disease on other therapies. It also appears to have a positive effect on self-reported quality of life, to reduce fatigue, and to improve language processing.

Following a suspension of the drug after two patients developed Progressive Multifocal Leukoencephalopathy (PML), an often-fatal viral infection of the brain, Tysabri was re-released. All patients now receive the drug through safety monitoring programs such as the Tysabri Outreach: Unified Commitment to Health (TOUCH™) Prescribing Program with registered infusion centers and pharmacies; and the international Tysabri Global Observation Program in Safety (TYGRUS). More than 55 cases of PML have now been reported. Studies are ongoing to see if it is possible to predict which individuals may be at risk for this condition, such as an antibody test for the virus that causes PML. In MS patients, no cases of PML have occurred prior to 12 months of continuous use.

The drug shows continued effectiveness (as measured by a reduction in relapses), favorable MRI data, and a reduction in progression of disability (as indicated by an improvement in EDSS). It also shows promise as a therapy in patients who had a previously poor response to other disease-modifying therapies. It significantly improves the patients' perception of health-related quality of life, reduces MS-associated pain, has at least a mild positive effect on fatigue and depression, improves cognitive function, and may reduce loss of vision associated with RRMS.

The Phase III SURPASS trial is evaluating 1,800 individuals with RRMS who have been treated earlier with either Rebif or Copaxone, and are then switched to Tysabri after continuing to experience relapses. The study began in February 2010 and is scheduled for completion in May 2013. The primary outcome measure is the annualized relapse rate; secondary measures include changes in T2-lesion volume, the proportion of subjects free from disease activity, and the change in patient-perceived physical status.

The multinational STRATA study is evaluating efficacy and safety. It involves patients who participated in the earlier AFFIRM, SENTINEL, and GLANCE studies. The risk of PML appeared to increase with continued exposure to Tysabri.

In addition to the risk of PML, side effects with Tysabri include liver damage, a three-fold increased incidence of Herpes zoster infections, occasional infections of a variety of types, and rare instances of anemia that are easily treatable. Individuals taking Tysabri are closely monitored by their healthcare team to watch for adverse events and provide immediate treatment if needed.

FDA-APPROVED MEDICATIONS

Novantrone® *(mitoxantrone)*

Parent company: *EMD Serono, Inc.*

Given via intravenous infusion, the dose varies according to an individual's weight. It is administered once every three months for a maximum of two-to-three years. The total dose that can be taken is limited to avoid the risk of damage to the heart. Careful monitoring both during and after treatment is necessary.

Novantrone is approved for use in SPMS, progressive-relapsing MS (PRMS), worsening RRMS, and people who are not responding favorably to standard therapies.

This drug appears to delay the time to a first-treated relapse, reduces the number of relapses, delays the time to disability progression, and decreases the number of new lesions that can be detected by MRI. It also appears to stabilize disease activity in some individuals with SPMS.

Novantrone is an immunosuppressant that has been used for years to treat cancer. It targets rapidly dividing cells, including those believed to be involved in MS. Side effects may include cardiac disease and leukemia; patients must be closely

monitored to minimize these risks. Chemotherapy-induced amenorrhea (cessation of periods) was seen in about one-fourth of treated women. Use in the United States is declining due to these side effects.

EXPERIMENTAL ORAL MEDICATIONS

Cladribine

Parent company: *EMD Serono, Inc.*

Given orally, as one or two courses a year, depending on the study regimen.

The FDA gave Fast Track approval status to cladribine in July 2010, and the drug may be available in the first quarter of 2011.

This drug predominantly affects peripheral blood lymphocytes, with relative preservation of other cell types and components. It causes a preferential and sustained depletion of certain T cells in the immune system, as well as a decrease in B cells. (T and B cells are two types of lymphocytes, which help to keep the body free of infections and cancer.) Cladribine also seems to directly influence the overall T-cell response.

In a large-scale Phase III clinical trial, cladribine significantly reduced relapse rates and other disease activity in people with relapsing-remitting MS.

The two-year Phase III CLARITY trial of two levels of cladribine versus placebo involved 1,326 patients with RRMS. Each course

EXPERIMENTAL ORAL MEDICATIONS

Cladribine *(continued)*

consisted of once daily administration for four to five consecutive days, and study participants took cladribine for a total of eight to 20 days of treatment during the year. It met its primary endpoint, showing 55- to 58-percent reductions in annualized relapse rates, a 31- to 33-percent reduction in disability progression, and a substantial reduction in lesion burden. No clinical relapses were seen in 79 to 80 percent of the treated group, as compared to 61 percent in the placebo group. In the ongoing two-year extension study, all participants will receive cladribine; it will continue to assess safety, tolerability and effect on progression of disability.

Detailed study data were released in the spring of 2010 at the American Academy of Neurology and Consortium of MS Centers meetings. Conclusions included that treatment with cladribine resulted in an early onset of effect in MRI and clinical outcomes. MRI evidence of disease activity was reduced by both cladribine regimens. The MRI findings were accompanied by significant improvements in clinical outcomes and a favorable safety profile. Additionally, a substantial proportion of patients achieved a disease activity–free status over 96 weeks.

Its safety in pregnancy will be determined by the FDA in its final review.

The long-term safety of cladribine will be tested in the eight-year PREMIERE registry. It will provide long-term active safety and risk-benefit information.

Some patients with aggressive MS failed to respond clinically and by MRI after two short courses of cladribine. A reduction of T- or B-lymphocyte counts was not seen in these patients. It may be that some patients with aggressive MS disease are resistant to cladribine, may require additional courses to reduce relapses or MRI activity, or may require additional courses to cause a reduction of lymphocyte count which may be tied to the efficacy of the drug. A larger cohort of patients with aggressive MS is being followed to expand these findings.

The ONWARD Phase II study of 200 individuals who have experienced at least one relapse while taking Rebif is now recruiting. This study combines oral cladribine with Rebif, to determine whether the combination is more effective than Rebif alone.

The Phase III ORACLE MS study is ongoing, and will assess whether cladribine can delay the time to a second clinical demyelinating attack in 600 individuals who have had a first clinical demyelinating event (CIS). The study will be complete in October 2012.

The main risk of a side effect with cladribine is the potential for developing infections, most commonly Herpes infections.
A prolonged decrease in white blood cells has also been seen in some patients.
The FDA will further evaluate other side effects and risks.

EXPERIMENTAL ORAL MEDICATIONS

Laquinimod

Parent company: *Teva Neuroscience, Inc. and Active Biotech*

Oral medication; 0.6 mg taken once daily. It has been granted Fast Track status by the FDA.

Laquinimod is being studied in RRMS. Although its exact mechanisms of action are unknown, it is an immunomodulator, apparently via its effects on cytokines and interleukins. It also appears to reduce white blood cell penetration of the CNS. In addition to its immunomodulatory actions, laquinimod increases levels of the brain-derived neurotrophic factor (BDNF). BDNF may contribute to neuroprotection in MS patients.

A 36-week Phase II trial showed a 40-percent reduction in disease activity as measured by MRI, a trend toward reduction in annual relapse rates, and a delay in the time to first relapse. The drug was well tolerated.

The ongoing placebo-controlled ALLEGRO study of 1,000 individuals will determine the efficacy of daily oral treatment with laquinimod in RRMS versus placebo. Its outcome measures include the number of confirmed relapses, the accumulation of physical disability, and MRI changes during the two-year study period. The study began in February 2007 and is scheduled for completion in February 2011.

Enrollment has been completed for the BRAVO Phase III pivotal trial with 1,200 patients. BRAVO is a global, 24-month, double-blind study designed to evaluate the efficacy, safety, and tolerability versus placebo. It will also provide risk-benefit data for laquinimod versus Avonex. Outcome measures are relapse rate, the accumulation of disability, and disease activity on MRI. The study is scheduled for completion in June 2011. A second large global phase III trial is now beginning enrollment.

Teriflunomide

Parent company: *Sanofi-Aventis*

Oral medication taken daily.

This drug is an immunomodulator that affects both T and B-cell proliferation. It inhibits rapidly dividing cells, including activated T cells, which are thought to drive the disease process in MS. It also appears to inhibit nerve degeneration by reducing the production of free radicals by macrophages and astrocytes. Unlike similar drugs, it is not thought to affect other immune functions, possibly providing patients with a decreased risk of infections and other complications linked to chemotherapy-like drugs.

A Phase II trial of RRMS evaluated two dose levels versus placebo. The treated groups had significantly fewer enhancing lesions and a lower relapse rate; fewer patients in the high-dose group experienced an increase in disability versus placebo, and there was a trend toward more relapse-free patients. Treatment was well tolerated. Side effects included infections, especially

EXPERIMENTAL ORAL MEDICATIONS

Teriflunomide *(continued)*

respiratory, but these were not serious.

The TEMSO trial for RRMS is comparing 7 and 14 mg of teriflunomide in 1,080 individuals. The primary endpoint is relapse rate; secondary measures include time to progression of disability, total disease burden on MRI, and subject-reported fatigue. The study was completed in July 2010; results are not yet available.

The TOWER efficacy study of 1,110 individuals with RRMS is now enrolling and is scheduled for completion in September 2011. It will test 7 and 14 mg doses versus placebo. Its primary endpoint is relapse rate; the secondary endpoint is time to disability progression.

The ongoing TOPIC study of 780 individuals with CIS, also compares 7 and 14 mg active drug versus placebo. The study began in February 2008 and its primary endpoint is the time of conversion to clinically-definite MS. Secondary endpoints include burden of disease and other MRI variables, relapse rate, the proportion of disability-free patients, and the drug's safety and tolerability.

Phase II combination studies of teriflunomide added to interferon and Copaxone in clinically stable patients have been completed. Both studies evaluated tolerability and safety, the number of gadolinium-enhancing lesions, and burden of disease on MRI. Combined treatment with teriflunomide appears to be superior to interferon alone in reducing lesion load. No significant difference was seen in relapse rate, although a trend was found toward improvement in the combination group. The combination with Copaxone, although primarily a safety study, showed a reduction in the number and size of lesions as seen on an MRI.

BG-12 *(dimethyl fumerate)*

Parent company: *Biogen Idec*

Oral medication taken daily.

This drug may have a distinct dual mechanism of action. First, it is an immunomodulator with anti-inflammatory properties. This induces inflammatory cytokines and appears to suppress damaging macrophage activity (immune cells that stimulate lymphocytes) as part of its anti-inflammatory activity. Second, BG-12 may also have neuroprotective effects. This is due to its activation of a substance that is critical for resistance to cellular damage from what is termed "oxidative stress" as well as for normal immune function. BG-12 is being studied in RRMS.

The ongoing Phase III DEFINE and CONFIRM studies are no longer enrolling participants and these studies will be completed in December 2010 and April 2011, respectively. The DEFINE study is comparing two doses of BG-12 against placebo in 1,011 patients. The primary outcome measure is the proportion of patients who experience relapses. The CONFIRM study is testing two levels of the drug against Copaxone and placebo in 1,232 patients, with the primary measure of the reduction in relapse rate.

EXPERIMENTAL ORAL MEDICATIONS

BG-12 *(continued)*

The Phase II EXPLORE trial will evaluate oral BG-12 as a combination therapy for patients who continue to experience disease progression despite ongoing treatment. It will evaluate the safety and tolerability of BG-12 when administered with interferons or Copaxone to 100 people who continue to have evidence of disease activity (despite receiving consistent monotherapy for at least a year). Efficacy endpoints will also be assessed in a subset of participants.

Trials to date indicate that the drug is safe and that its overall tolerability improves with continued use. A long-term Phase III efficacy and safety study is enrolling approximately 1,700 individuals who participated in earlier trials.

Side effects include skin flushing and gastrointestinal symptoms.

Statins

Statins are oral medications most commonly prescribed to lower cholesterol. Current interest is based on the observation that the risk of developing new brain lesions was reduced by about 50 percent if patients with early forms of MS were taking atorvastatin (Lipitor®).

Combination Studies:
In one study, the combination of Rebif with atorvastatin increased MRI and clinical disease activity, suggesting that statins may block the therapeutic effects of interferons. However, the two studies below did not support this, and more data are needed.

A small Phase II study that added atorvastatin to Avonex in 30 patients with CIS indicated a significant reduction of new T2 lesions in those on combination therapy. Although the primary endpoint of the study was not met, other data in the study were encouraging.

A small Danish Phase III study of 64 patients is examining simvastatin as an add-on treatment to Copaxone in RRMS. The study, which has 20 participants, began in March 2008 and is scheduled for completion in March 2011. The primary outcome measure is the number of new and/or enlarging lesions on MRI; secondary measures include changes in the EDSS score and the number of documented relapses.

EXPERIMENTAL MONOCLONAL ANTIBODY MEDICATIONS

Campath® *(alemtuzumab)*

Parent companies: *Genzyme Corporation and Bayer HealthCare Pharmaceuticals*

Administered in one course yearly by intravenous infusion over three-to-five consecutive days. The drug is approved for the treatment of B-cell leukemia and targets T cells, B cells, and macrophages.

The drug was granted Fast Track status by the FDA in June 2010, which will expedite its review.

The CAMMS223 Phase II study of 334 individuals with early, active RRMS compared Campath to high-dose Rebif (44 mcg) in RRMS. In a three-year safety and efficacy trial, Campath was more effective than interferon beta-1a at reducing the relapse rate and the risk for 60-month sustained accumulation of disability in patients with RRMS. In fact, the annualized relapse rate in patients on Campath was 0.1, which means one attack every 10 years. This is the lowest relapse rate ever reported for an MS drug. More than 50 percent of the Campath-treated patients actually improved.

In a fourth-year extension study of 334 individuals who participated in the original CARE MS1 and CARE MS2 studies, Campath yielded a 73-percent reduction in risk for sustained accumulation of disability versus a 68-percent reduction for individuals taking interferon beta-1a. At year four, 77 percent of Campath-treated patients were relapse-free, compared with 49 percent of patients taking interferon beta-1a.

Side effects include a reduction in blood clotting, thyroid disorders, infusion reactions, and infection. Patients need to be monitored closely due to risk of significant toxicities.

Zenapax® *(daclizumab)*

Parent companies: *Biogen Idec and PDL BioPharma*

Administered via intravenous infusion every four weeks; also studied in subcutaneous injections.

Zenapax is a genetically engineered monoclonal antibody that binds to a specific receptor on T cells for interleukin-2 (IL-2), which plays a role in the activation of T and B cells. It results in a sustained but reversible reduction in activated T cells and reduces inflammation. It is approved by the FDA for use in rheumatoid arthritis and other autoimmune diseases.

Participants in the Phase II CHOICE study had either RRMS or SPMS, with worsening disease activity while on interferon-beta therapy. The study showed that Zenapax was well tolerated when added to the interferon. A 25-percent reduction was seen in the frequency of enhancing lesions in the low-dose group (150 mg every four weeks), and a 72-percent reduction was seen in the high-dose group (300 mg every four weeks).

The ongoing Phase II SELECT extension trial, with 600 participants, is scheduled for completion in September 2015. It is a one-year study that will assess the safety and immunogenicity (the incidence of the

EXPERIMENTAL MONOCLONAL ANTIBODY MEDICATIONS

Zenapax (continued)

development of antibodies) of extended treatment with Zenapax. The study will assess adverse events, laboratory evaluations, vital signs, physical examinations, and the development of antibodies. Secondary outcome measures include the continuing response to treatment as measured by MRI and clinically (determining annualized relapse rate and the proportion of subjects who are relapse-free).

Rituxan® (rituximab)

Parent companies: *Genentech and Biogen Idec*

Administered via intravenous infusion.

Rituxan is a monoclonal antibody that binds to a receptor on the surface of B cells. These cells are then destroyed and their levels in the circulation are decreased.

A Phase II trial examined the effect of a single course of treatment; with two infusions of 1,000 mg each, administered two weeks apart. At 24 and 48 weeks, the number of active lesions was reduced by 91 percent and relapses were reduced by 58 percent.

The drug has also been tested in 26 people with RRMS who experienced continued clinical activity despite treatment with one of the approved disease-modifying therapies. During the 24 weeks of the trial, participants received four doses of Rituxan while continuing to take their same medication. Participants showed statistically significant improvement in their MS Functional Composite Scores.

Serious adverse events, including PML (as with Tysabri), have been reported in patients treated with Rituxan for diseases other than MS; patients must be closely monitored.

Ocrelizumab

Parent companies: *Genentech (in collaboration with Roche Pharma AG)*

Ocrelizumab is administered via intravenous infusion.

Like Rituxan, this drug is an anti-CD20 monoclonal antibody. It has the potential advantage of being more like human antibody than Rituxan.

A Phase II study, with 250 participants, is ongoing. It will compare the treatment with Ocrelizumab versus Avonex and placebo; all treatment arms include the repeated IV administration of methylprednisolone. The primary outcome measure is the total number of gadolinium-enhancing T1 lesions as observed on MRI scans of the brain. Secondary outcome measures include the annualized relapse rate, the proportion of patients who remain relapse-free, and the change in total volume of T2 lesions on MRI scans of the brain.

The study began in April 2008 and is estimated to be completed in January 2012.

"I DECIDED TO GO WITH BETASERON®."

BETASERON® (INTERFERON BETA-1b)
MEDICATION + SUPPORT™

Early treatment with BETASERON® (interferon beta-1b) may help delay progression of CIS or relapsing forms of multiple sclerosis (MS).[1] And that's important, because even though you may be feeling fine, MS can cause serious "silent" damage in its early stages.[2]

What's more, BETASERON is offered with BETAPLUS®, the support program rated best* by physicians. Plus, you get 24/7 access to an MS-trained BETA Nurse assigned to you, and $0 monthly copay.**

Find out if BETASERON is right for you. Talk to your healthcare team, visit BETASERON.com or call 1-800-788-1467.

INDICATIONS AND USAGE

BETASERON® (interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

IMPORTANT SAFETY INFORMATION

The most commonly reported adverse reactions are lymphopenia (low numbers of a certain kind of white blood cell), injection-site reaction, asthenia (general weakness), flu-like symptom complex (flu syndrome and/or a combination of at least two adverse events [AEs] from fever, chills, muscle aches, tiredness and sweating), headache and pain. Gradual dose titration and use of analgesics during treatment initiation may help reduce flu-like symptoms. **BETASERON** should be used with caution in patients with depression. Injection-site necrosis has been reported in 4% of patients in controlled trials. Patients should be advised of the importance of rotating injection sites. Female patients should be warned about the potential risk to pregnancy. Cases of anaphylaxis have been reported rarely.

See "Warnings", "Precautions" and "Adverse Reactions" sections of full Prescribing Information. More information, including the full Prescribing Information, is available at **www.BETASERON.com**.

Please see accompanying Medication Guide and full Prescribing Information.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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* In a survey of 199 physicians conducted by JZM/Phoenix Healthcare Practice, BETAPLUS, an MS patient support program for those on BETASERON, was rated "best" for affordable therapy, copay assistance, and nurse access and training, compared to MS support programs for Avonex®, Copaxone®, and Rebif®. *Attitude, Awareness and Use Tracking Study Among Physicians*, June 2008.

** Some restrictions apply. Copay assistance is limited to $9500 per patient per calendar year. Patients who are enrolled in any type of government insurance or reimbursement programs are not eligible. As a condition precedent of the copayment support provided under this program, eg, copay refunds, participating patients and pharmacies are obligated to inform insurance companies and third-party payors of any benefits they receive and the value of this program, as required by contract or otherwise. Void where prohibited by law, taxed, or restricted. Patients enrolled in Bayer's Patient Assistance Program are not eligible.

References: 1. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology*. 2006;67:1242-1249. **2.** Adherence. National Multiple Sclerosis Society Web site. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/adherence/index.aspx. Accessed June 7, 2010

Bayer HealthCare Pharmaceuticals

BETASERON®
(INTERFERON BETA-1b) FOR SC INJECTION
6800503BS

Brief Summary of Medication Guide

Betaseron® (bay-ta-seer-on)

Interferon beta-1b
(in-ter-feer-on beta-one-be)

Please read this leaflet carefully before you start to use Betaseron® and each time your prescription is refilled since there may be new information. The information in this medication guide does not take the place of talking with your doctor or healthcare professional.

What is the most important information I should know about Betaseron?

Betaseron will not cure multiple sclerosis (MS) but it has been shown to decrease the number of flare-ups of the disease. Betaseron can cause serious side effects, so before you start taking Betaseron, you should talk to your doctor about the possible benefits of Betaseron and its possible side effects to decide if Betaseron is right for you. Potential serious side effects include:

- **Depression.** Some patients treated with interferons, including Betaseron, have become seriously depressed (feeling sad). Some patients have thought about or have attempted to kill themselves. Depression (a sinking of spirits or sadness) is not uncommon in people with multiple sclerosis. However, if you are feeling noticeably sadder or helpless, or feel like hurting yourself or others, you should tell a family member or friend right away and call your doctor or health care provider as soon as possible. Your doctor may ask that you stop using Betaseron. Before starting Betaseron, you should also tell your doctor if you have ever had any mental illness, including depression, and if you take any medications for depression.
- **Liver problems.** Your liver may be affected by taking Betaseron and a few patients have developed severe liver injury. Your healthcare provider may ask you to have regular blood tests to make sure that your liver is working properly. If your skin or the whites of your eyes become yellow or if you are bruising easily, you should call your doctor immediately.
- **Risk to pregnancy.** If you become pregnant while taking Betaseron you should stop using Betaseron immediately and call your doctor. Betaseron may cause you to lose your baby (miscarry) or may cause harm to your unborn child. You and your doctor will need to decide whether the potential benefit of taking Betaseron is greater than the potential risks to your unborn child.

  A pregnancy registry has been established to monitor pregnancy outcomes of women exposed to Betaseron while pregnant. Providers are encouraged to obtain information on line at www.BetaseronPregnancyRegistry.com and register patients by calling 1-800-478-7049.
- **Allergic reactions.** Some patients taking Betaseron have had severe allergic reactions leading to difficulty breathing and swallowing; these reactions can happen quickly. Allergic reactions can happen after your first dose or may not happen until after you have taken Betaseron many times. Less severe allergic reactions such as rash, itching, skin bumps or swelling of the mouth and tongue can also happen. If you think you are having an allergic reaction, stop using Betaseron immediately and call your doctor.
- **Injection site problems.** Betaseron may cause redness, pain or swelling at the place where an injection was given. A few patients have developed skin infections or areas of severe skin damage (necrosis). If one of your injection sites becomes swollen and painful or the area looks infected and it doesn't heal within a few days, you should call your doctor.
- **Seizures -** Some patients have had seizures while taking Betaseron, including some patients who have never had seizures before. It is not known whether the seizures were related to the effects of their MS, to Betaseron, or to a combination of both. If you have a seizure while taking Betaseron, you should stop taking Betaseron and call your doctor right away.
- **Heart problems -** While Betaseron is not known to have direct effects on the heart, a few patients who did not have a history of heart problems developed heart muscle problems or congestive heart failure after taking Betaseron. Some of the symptoms of heart problems are swollen ankles, shortness of breath, decreased ability to exercise, fast heartbeat, tightness in chest, increased need to urinate at night, and not being able to lay flat in bed. If you develop these symptoms or any heart problems while taking Betaseron, you should call your doctor right away.

For more information on possible side effects with Betaseron, please read the section on **"What are the possible side effects of Betaseron?"** in this Medication Guide.

What is Betaseron?

Betaseron is a type of protein called beta interferon that occurs naturally in the body. It is used to treat relapsing forms of multiple sclerosis. It will not cure your MS but may decrease the number of flare-ups of the disease. MS is a lifelong disease that affects your nervous system by destroying the protective covering (myelin) that surrounds your nerve fibers. The way Betaseron works in MS is not known.

Who should not take Betaseron?

Do not take Betaseron if you:

- Have had allergic reactions such as difficulty breathing, flushing or hives to another interferon beta or to human albumin.

If you have any of the following conditions or serious medical problems, you should tell your doctor *before* taking Betaseron:

- Depression (a sinking feeling or sadness), anxiety (feeling uneasy, nervous, or fearful for no reason), or trouble sleeping
- Liver diseases
- Problems with your thyroid gland
- Blood problems such as bleeding or bruising easily and anemia (low red blood cells) or low white blood cells
- Epilepsy
- Heart problems
- Are pregnant, breast feeding, or planning to become pregnant

You should tell your doctor if you are taking any other prescription or nonprescription medicines. This includes any vitamin or mineral supplements, or herbal products.

How should I take Betaseron?

Betaseron is given by injection under the skin (subcutaneous injection) every other day. Your injections should be approximately 48 hours (two days) apart, so it is best to take them at the same time each day, preferably in the evening just before bedtime.

You may be started on a lower dose when you first start taking Betaseron. Your doctor will tell you what dose of Betaseron to use, and that dose may change based on how your body responds. You should not change your dose without talking with your doctor.

If you miss a dose, you should take your next dose as soon as you remember or are able to take it. Your next injection should be taken about 48 hours (two days) after that dose. **Do not take Betaseron on two consecutive days.** If you accidentally take more than your prescribed dose, or take it on two consecutive days, call your doctor right away.

You should always follow your doctor's instructions and advice about how to take this medication. If your doctor feels that you, or a family member or friend may give you the injections, then you and/or the other person should be trained by your doctor or healthcare provider in how to give an injection. Do not try to give yourself (or have another person give you) injections at home until you (or both of you) understand and are comfortable with how to prepare your dose and give the injection.

Always use a new, unopened, vial of Betaseron and syringe for each injection. Never reuse vials or syringes.

It is important that you change your injection site each time Betaseron is injected. This will lessen the chance of your having a serious skin reaction at the spot where you inject Betaseron. You should always avoid injecting Betaseron into an area of skin that is sore, reddened, infected or otherwise damaged.

At the end of this leaflet there are detailed instructions on how to prepare and give an injection of Betaseron. You should become familiar with these instructions and follow your doctor's orders before injecting Betaseron.

What should I avoid while taking Betaseron?

- **Pregnancy.** You should avoid becoming pregnant while taking Betaseron until you have talked with your doctor. Betaseron can cause you to lose your baby (miscarry).
- **Breast feeding.** You should talk to your doctor if you are breast feeding an infant. It is not known if the interferon in Betaseron can be passed to an infant in mother's milk, and it is not known whether the drug could harm the infant if it is passed to an infant.

What are the possible side effects of Betaseron?

- **Flu-like symptoms.** Most patients have flu-like symptoms (fever, chills, sweating, muscle aches and tiredness). For many patients, these symptoms will lessen or go away over time. You should talk to your doctor about whether you should take an over the counter medication for pain or fever reduction before or after taking your dose of Betaseron.
- Skin reactions. Soreness, redness, pain, bruising or swelling may occur at the place of injection **(see "What is the most important information I should know about Betaseron?").**
- **Depression and anxiety.** Some patients taking interferons have become very depressed and/or anxious. There have been patients taking interferons who have had thoughts about killing themselves. If you feel sad or hopeless you should tell a friend or family member right away and call your doctor immediately. **(see "*What is the most important information I should know about Betaseron*?").**
- **Liver problems.** Your liver function may be affected. If you develop symptoms of changes in your liver, including yellowing of the skin and whites of the eyes and easy bruising, call your doctor immediately. **(see "What is the most important information I should know about Betaseron?")**
- **Blood problems.** You may have a drop in the levels of infection-fighting white blood cells, red blood cells, or cells that help you form blood clots. If drops in levels are severe, they can lessen your ability to fight infections, make you feel tired or sluggish or cause you to bruise or bleed easily.
- **Thyroid problems.** Your thyroid function may change. Symptoms of changes in the function of your thyroid include feeling cold or hot much of the time or change in your weight (gain or loss) without a change in your diet or amount of exercise you are getting.
- **Allergic reaction.** Some patients have had hives, rash, skin bumps or itching while they were taking Betaseron. There is also a rare possibility that you can have a life-threatening allergic reaction. **(see "*What is the most important information I should know about Betaseron*?").**
- **Seizures -** Some patients have had seizures while taking Betaseron, including patients who have never had seizures before. It is not known whether the seizures were related to the effects of their MS, to Betaseron, or to a combination of both. If you have a seizure while taking Betaseron, you should call your doctor right away. **(See "What is the most important information I should know about Betaseron?")**
- **Heart problems -** While Betaseron is not known to have any direct effects on the heart, a few patients who did not have a history of heart problems developed heart muscle problems or congestive heart failure after taking Betaseron. Some of the symptoms of heart problems are swollen ankles, shortness of breath, decreased ability to exercise, fast heartbeat, tightness in chest, increased need to urinate at night, and not being able to lay flat in bed. If you develop these symptoms or any heart problems while taking Betaseron, you should call your doctor right away. **(See "What is the most important information I should know about Betaseron?")**

Whether you experience any of these side effects or not, you and your doctor should periodically talk about your general health. Your doctor may want to monitor you more closely and ask you to have blood tests done more frequently.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General Information About Prescription Medicines

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This medication has been prescribed for your particular medical condition. Do not use it for another condition or give this drug to anyone else. If you have any questions you should speak with your doctor or health care professional. You may also ask your doctor or pharmacist for a copy of the information provided to them with the product. Keep this and all drugs out of the reach of children.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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OTHER THERAPIES IN DEVELOPMENT

Dirucotide *(MBP8298)*

Recent studies did not show efficacy, and further development of this drug for use in MS has been discontinued.

Tovaxin™

Parent companies: *Opexa Therapeutics*

This is a T-cell vaccine given via subcutaneous injection every four weeks. In this process, myelin-reactive T cells are removed from a small amount of the patient's blood, inactivated, and then injected back into the patient. The body's immune system then protects the myelin from these cells.

A Phase II study showed significant improvements in the annualized relapse rate of patients with RRMS or SPMS. A decrease in myelin-reactive T cells in the blood was also found.

TERMS is an ongoing placebo-controlled one-year study in patients with CIS and RRMS to evaluate Tovaxin's efficacy, safety and tolerability. Patients in the trial also participated in an open-label, one-year extension study. The treatment was found to be safe, but did not achieve statistical significance in the primary endpoint, which was a reduction in the cumulative number of gadolinium-enhancing lesions as compared to placebo. Therefore, a larger study in RRMS patients is planned.

Vitamin D3

Vitamin D is a type of hormone and a powerful mediator of immune function. The data documenting an association between low vitamin D and high MS risk, relapses, disability and CNS inflammation now appear to be strong, consistent and reproducible.

Data from a number of lines of investigation suggest that vitamin D may be one underlying common factor that begins to make sense of the large body of data on the geographic distribution of susceptibility to MS, including the north-south gradient of distribution and the migration data indicating that where people live during the first fifteen years or so of life affects the incidence of the disease.

Genetically, a link appears to exist between alterations in the genes involved in vitamin D hormone synthesis and the vitamin D hormone receptor to MS risk. The strongest genetic risk factor for MS is a specific gene (HLA DRB1*1501), whose activity appears to be influenced by vitamin D.

A small study of 18 patients with RRMS published in early 2010 compared very high-dosage vitamin D3 (up to 40,000 IU daily versus supplementation with up to 4,000 IU). After one year, 38 percent of the control group (those not taking high-dose vitamin D3) had an increase in disability, versus only 8 percent of the treatment group.

OTHER THERAPIES IN DEVELOPMENT

Vitamin D3 *(continued)*

In another study, mice treated with vitamin D prior to the induction of EAE (an MS-like condition in animals) did not develop its symptoms. This is compared with a 100-percent incidence of symptom development in untreated mice.

A study looked at the effect on MS of maternal vitamin D exposure during pregnancy. This study was conducted with a group of 35,794 nurses whose mothers participated in the Nurses' Mothers' Study. The findings were consistent with a protective effect of maternal milk and vitamin D intake on the risk of developing MS.

Lower serum vitamin D3 levels have been associated with a substantially increased subsequent relapse rate in individuals with pediatric-onset MS or CIS. A clinical trial is needed to determine whether vitamin D supplementation might improve the course of the disease in these groups.

An Australian study found that people with CIS had less cumulative skin damage caused by the sun than non-MS controls, suggesting that they had less sun exposure. In a Canadian study of children who had experienced a single neurologic episode, the 16 percent who went on to develop MS had significantly lower vitamin D levels than those who did not.

Evidence is beginning to accumulate of a complex interaction between genetic susceptibility to MS and the role of vitamin D. The risk of developing MS is three times higher among those who carry a single copy of a specific gene variant and 10 times higher in those carrying two copies of the gene, which appears to be involved in the immune system. Proteins activated by vitamin D bind to and alter the function of a section of the chromosome near this gene, suggesting that vitamin D deficiency during pregnancy might alter the function of fetal genes, predisposing children to MS. The gene contains a "switch" that is activated by one form of vitamin D; this gene was missing from the variants not associated with MS.

BHT-3009

Parent companies: *Bayhill Therapeutics*

This DNA vaccine to myelin basic protein (MBP) contains the gene for MBP and is administered by intramuscular injection. This therapy is designed to cause immune tolerance, by reprogramming the immune system to modulate the response of the antigen-specific immune cells involved with MS. This would reduce the attack against the MBP in the myelin sheath.

Studies to date indicate that this vaccine is safe and well tolerated. BHT-3009 continued to demonstrate an excellent safety profile 13 months after the last dose, and reported safety data is similar to that found during the 44-week treatment phase.

A recent study indicated that a decrease in total brain lesions was maintained seven months after the last dose, with an improvement in the number of lesion-free patients and a reduction in the average number of lesions for all patients. No

OTHER THERAPIES IN DEVELOPMENT

BHT-3009 *(continued)*

treatment-related serious adverse events occurred, and more than 95 percent of all adverse events were mild to moderate. Survey protocol data on BHT-3009 demonstrate continued improvement in both MRI findings and relapse rates in patients with RRMS. Bayhill is currently discussing Phase III studies with potential partners.

Tetracycline Antibiotics

The tetracycline antibiotics, including minocycline and doxycycline, have immunomodulatory and neuroprotective activities. They appear to decrease the passage of leukocytes across the blood-brain barrier. An earlier trial of Copaxone plus minocycline showed favorable MRI data.

In a small trial in patients with RRMS, minocycline decreased gadolinium-enhancing activity by 50 percent over a period of six months. A subsequent 24-month trial showed a significant decrease in lesion activity and clinical status.

A Phase III trial that began in 2008 is studying the effect of 100 mg of oral minocycline twice daily on the conversion of CIS to a diagnosis of MS at six and 24 months.

A small Phase IIa study with 45 patients will study minocycline in acute optic neuritis (ON). It began in February 2010, and is scheduled for completion in February 2013. The primary aim of this open-label pilot trial is to estimate the treatment effect of 100 mg of oral minocycline twice daily for 90 days, initiated within 30 days of onset of ON. The study will evaluate the effects on functional and structural optic nerve recovery compared to no treatment. The primary outcome measure will be the degree of optic nerve recovery, as measured by the retinal nerve fiber thickness.

A small Phase IV study combining doxycycline with Avonex demonstrated a statistically significant reduction of gadolinium-enhancing lesions compared with Avonex alone. A larger trial is needed to confirm these results.

NEW DIRECTIONS IN MS RESEARCH

Predicting the Response to Treatment

Researchers continue to look for factors that may predict a positive or negative long-term outcome from a disease-modifying therapy. For example, a multi-center study of both mice with EAE (an MS-like condition in animals) and patients with RRMS showed that interferon-beta was effective in reducing EAE symptoms in disease induced by one type of T cells (T helper type 1), but that it exacerbated disease induced by another type of T cells (T helper 17 cells).

Effective treatment correlated with increases in interleukin-10 in the mice whose EAE was the result of the type 1 cells. In RRMS patients, non-responders to interferon-beta had higher interleukin-17 concentrations in their serum compared to responders. The researchers concluded that a high level of interleukin-17 in the serum of people with RRMS is associated with non-responsiveness to interferon-beta therapy.

Genetic differences also appear to exist between individuals who respond to interferon-beta treatment and those who do not. An Irish study which looks at how DNA relates to relapse rate and interferon treatment, and a German study which identifies the genes affected by interferon treatment, are noted in the following section.

Genetic Studies

A study from Ireland found that a slight variant in the DNA (single-nucleotide polymorphism) predicts how early a relapse may occur while on interferon-beta treatment. Potentially, this may help clinicians identify individuals who are less likely to respond to treatment.

In the spring of 2010, findings from a German study indicated that the function of 121 genes were altered by interferon beta-1a treatment, with 11 being especially prominent in terms of altering activity. This is a step toward eventually having the ability to predict which patients may or may not be expected to respond to a specific therapy.

Slight genetic variants may also explain why African-Americans tend to have a more aggressive disease progression than Caucasians and may be less responsive to interferon-beta treatment.

Australian researchers have discovered two new locations of genes that are linked to genetic susceptibility for MS. They also indicate a link between genetic susceptibility to MS and other autoimmune diseases, including Type 1 diabetes, rheumatoid arthritis, and Graves' disease (a thyroid disorder). The new gene locations also indicate the potential involvement of vitamin D metabolism (please see page 27).

New Therapies under Investigation

The earlier listing of approved and experimental drugs is only a fraction of the many treatments currently in development. Some of the following are among the most exciting potential therapies under investigation.

NEW DIRECTIONS IN MS RESEARCH

Neuroprotective agents: The term "neuroprotection" refers to strategies designed to prevent irreversible damage of a variety of cell types in the CNS, as well as to promote regeneration after MS-related damage has occurred, with the goal of preventing the development of disability. A variety of neuroprotective strategies are in the early stages of testing.

Some of the drugs thought to have neuroprotective activity appear to reduce damage by blocking sodium channels or by blocking the release of the damaging neurotransmitter glutamate. Some of these drugs may decrease the toxicity of free radicals in the brain. A number of research studies are ongoing on a wide variety of agents that may have neuroprotective effects. Some of these studies are discussed in previous sections on specific therapies.

A Phase II study now recruiting is designed to study the possible neuroprotective effect of **lamotrigine** and interferon beta-1a (Avonex given 30 mcg once weekly via intramuscular injection) in patients with RRMS. The study will focus on the safety of this combination.

An 18-month German study of **sunphenon epigallocatechin-gallate (egcg)** in patients with RRMS (SuniMS) is currently recruiting participants. Sunphenon is a green tea extract that contains 95-percent egcg. It will be given daily as an oral medication to determine whether it has anti-inflammatory and neuroprotective properties as assessed by MRI and clinical examination. Primary outcome measures include the number of new T2 lesions on an MRI of the brain; secondary outcome measures include the development of brain atrophy as well as safety and tolerability.

A Phase II study of **flupirtine** is still recruiting participants with RRMS. Flupirtine is a non-opioid analgesic drug that has been shown to have additional neuroprotective functions related to a reduction in the damaging glutamate neurotoxic pathway. The study began in December 2007 and has 80 participants; data collection will be completed in December 2010. Flupirtine is administered twice daily as an oral medication for a period of 12 months.

Neuroprotection is assessed by an MRI, magnetic resonance spectroscopy, optical coherence tomography, and clinical examination. The primary outcome measure is the cumulative number of new T2-hypertensive lesions on cranial magnetic resonance imaging. Secondary outcome measures include cerebral atrophy, the number of new and total gadolinium (Gd)-enhancing lesions, disease progression (as measured by the EDSS and MSFC), and retinal nerve fiber layer thickness, assessed by optical coherence tomography.

Bone-marrow derived, stem-cell transplantation: High-dose immunosuppressive therapy followed by transplantation of the patient's own bone-marrow-derived stem cells has been used to

NEW DIRECTIONS IN MS RESEARCH

prevent transplant rejection for many years. Taken from one's own bone marrow, this is the same type of stem cell that has been used in most MS studies – not to be confused with embryonic or other types of stem cells. The procedure is being tested in MS when very active disease continues while on a disease-modifying therapy. Evidence to date suggests that the therapy may be more successful in early stages of the disease.

In a Phase I/II study of 21 individuals with RRMS whose disease had continued to progress despite treatment with interferon-beta, 17 showed improvement of at least one point on the EDSS scale. Five of the 21 relapsed but achieved remission after further immunosuppression. After 37 months, all patients were free from progression, and 16 were free of relapses. Significant improvement was also seen in symptoms such as balance, walking and weakness, as well as self-reported quality of life.

A Phase I safety study being initiated at the Cleveland Clinic involves first removing and storing bone marrow cells, which are restored to the marrow after the patient's immune system is suppressed. This study involves approximately 24 participants with relapsing forms of MS (approximately equal numbers with RRMS and SPMS) and evidence of involvement of the visual system.

Mesenchymal stem cells (MSC) are cells derived from tissues other than bone marrow. A small study of autologous (derived from a person's own body) MSC transplantation is not yet open for participant recruitment and will have 24 participants. It is scheduled for completion in December 2013. The primary outcome measure is to evaluate infusion-related safety and tolerability; the secondary outcome measure is the effects on MS disease activity as measured by the number of Gd-enhancing brain MRI lesions.

Early data from a Pilot Phase I/II clinical trial in Israel suggest that intrathecal and intravenous injection of MSC is a clinically feasible and relatively safe procedure. The trial used autologous mesenchymal stem cells in 15 patients with MS and 19 with ALS. With the MS patients, the mean EDSS score improved from 6.7 to 5.9 after six months. Further controlled studies and longer observation periods are needed to evaluate long-term safety and potential clinical efficacy.

A Phase III study of **hematopoietic stem cell therapy** with 110 participants began in January 2008 and is expected to be completed in January 2012. (Hematopoietic stem cells are derived from the bone marrow and give rise to all of the blood cell types.) Participants will be selected based on failure to respond to previous interferon treatment. The study is currently recruiting participants. The primary outcome measure is progression in the EDSS over four years.

Sex hormones: Estriol is an estrogen-like hormone that may have both neuroprotective and anti-inflammatory properties. Its possible use in MS was suggested by the fact that women with MS tend to have fewer relapses

during pregnancy, but are often subject to relapses during the postpartum period, when the high levels of female steroid hormones present during pregnancy return to normal levels.

Parasites: Some evidence supports that infections such as gut parasites normally help to regulate immune activity, and that the increase in autoimmune diseases in industrialized countries may in part be an unintended consequence of improved hygiene. Ongoing studies selectively expose individuals with autoimmune disease, including MS, to these organisms.

As of August 2010, the Phase II study, "Helminth-induced Immunomodulation Therapy (HINT)," was recruiting 20 individuals with RRMS at the University of Wisconsin in Madison and the Marshfield Clinic. Participants will receive a dose of 2,500 ova (tiny eggs) in liquid form every two weeks. After this liquid is ingested, the eggs hatch and grow to the size of an eyelash within the digestive tract, but once in the large intestine, the body's immune system kills the larvae. The primary outcome measure is MS activity, as judged by the number of new gadolinium-enhancing lesions on serial MRI scans. The study is estimated to be completed in March 2011.

A Phase II study of **CDP323** was recently discontinued due to a lack of significant changes in MRI findings and possibly other clinical measures in the study population. CDP323 is an oral Tysabri-like drug that has a short half-life, meaning that it is removed naturally from the body more rapidly than Tysabri. It had been hoped that the drug would have less risk for PML than Tysabri. The cancelled study was evaluating the safety, tolerability and MRI effects of CDP323 as compared to placebo. No cases of PML (progressive multifocal leukoencephalopathy) were noted.

RTL1000 (recombinant T-cell receptor ligand) is a highly selective protein that inhibits the activation of myelin-reactive T cells, preventing the release of inflammatory cytokines and causing the release of anti-inflammatory cytokines. Preliminary results of a Phase I trial of patients with RRMS and SPMS reported in the spring of 2010 indicated that IV infusion at a dose of 60 mg is well tolerated. Although this study was not designed to assess efficacy, immunological data in a subgroup of patients indicated RTL1000 had positive effects on MRI and clinical disease indicators.

BAF312 is an S1P receptor modulator, one of the same class of drugs as fingolimod, that has been shown to reverse EAE in mice. Once-daily oral application of BAF312 was initiated during established, chronic EAE. It was associated with a remission of severe neurological paralysis and improved motor function in mice. In the same setting, Gilenya (fingolimod, 3 mg/kg orally once daily) and Copaxone (2 mg/mouse subcutaneously once daily) induced a 61-percent and a 19-percent reduction of clinical scores, respectively.

CS-0777 is another S1P receptor

modulator. It causes a transient, dose-dependent decrease in circulating lymphocytes and T and B cells.

A number of other agents have shown some encouraging immunomodulatory effects, either in animals or humans, and are under investigation for possible future use in MS. These include: **CGP77116**, which is a small protein similar to myelin basic protein (MBP) and designed to modify the immune reaction that destroys myelin; **SB-683699**, thought to reduce the number of active white blood cells entering the brain; **RG2007**, which may block a T-cell pathway involved in MS; **CS-0777**, an oral immunosuppressive drug in Phase I studies; **MK0812**, which targets proteins known as chemokines that attract immune-system cells to areas of inflammation; and **symadex**, which inhibits a pathway involved in macrophage maturation.

Atacicept (ATX-MS-1467) is a "cocktail" of four peptides derived from human myelin basic protein. It appears to block the development of mature B cells and inhibits the survival of antibody-producing cells. The drug is now in Phase II trials to evaluate its safety and tolerability, along with determining whether it reduces CNS inflammation in RRMS on MRI. It is administered via subcutaneous injection.

Anti-Lingo-1 (BIIB033) is a monoclonal antibody now being readied for its first human Phase I trial, and is presently enrolling participants. It will focus on safety and tolerability. The study started in January 2010 and is scheduled for completion in June 2011. The primary outcome of the study is to evaluate the safety and tolerability of a single dose of Anti-Lingo-1 given via IV infusion, administered to healthy adult volunteers. Previous animal studies showed that it promotes spinal cord remyelination and axonal integrity in the animal model of MS (EAE).

A small French study of **masitinib**, a drug which targets mast cells, was tested in 35 patients with either PPMS or SPMS. During 18 months of treatment, EDSS scores remained stable in both treated and placebo groups with PPMS. In the SPMS group, the treated individuals remained stable, while the placebo group averaged an increase of one EDSS point. This small population, "proof of concept" study (which refers to early studies, prior to phase III) suggests that targeting mast cells might provide a therapeutic option for both PPMS and SPMS patients. Data will give ground for a large-scale phase III trial.

MN-166 (ibudilast) is an orally administered small molecule with neuroprotective and anti-inflammatory properties. In the first year of a two-year study in individuals with RRMS, it significantly reduced the percentage of brain volume loss and prolonged time to first relapse by 157 days. It did not, however, significantly reduce cumulative new lesion count, which was the primary outcome measure of the study.

Do sudden, unpredictable outbursts of crying or laughing disrupt your life?

You are not alone.

You may be one of more than a million Americans suffering from Pseudobulbar Affect (PBA).

Pseudobulbar Affect can happen when disease or injury damages the area of the brain that controls how you express your emotions. The result: sudden, unpredictable crying or laughing that can be disruptive and embarrassing.

But you are not alone. PBA occurs in people with underlying neurologic disease or injury and is estimated to impact over a million patients and their caregivers.

You or someone you care for may experience these involuntary episodes if diagnosed with multiple sclerosis (MS), Lou Gehrig's disease (ALS), stroke, traumatic brain injury, or certain other neurologic conditions. PBA episodes may be caused by "short circuits" in brain signaling. It may not be depression. Learn more about how you might begin to take control.

Pseudobulbar Affect | PBA

To learn more, please visit www.PBAinfo.org

AVANIR pharmaceuticals

PBA-0018-ADV-1210

NEW DIRECTIONS IN MS RESEARCH

A Phase II study to evaluate the effectiveness of **oral recombinant ovine interferon tau** in RRMS indicated effectiveness in decreasing the number of new gadolinium-enhancing lesions during a nine-month period. It also appeared to be both safe and well-tolerated.

Closing Notes

In summary, the future of disease-modifying therapies (DMTs) for MS looks bright, both in terms of new information on currently approved DMTs, as well as exciting results for emerging therapies. For approved therapies, studies will continue to evaluate long-term effectiveness and safety, as well as their possible usefulness in combination therapies. With new treatments, because of their complex mechanisms of action and potential side effects, weighing the benefits against possible risks is vital.

Research is ongoing into a wide variety of experimental therapies, including those that may be effective for individuals with the progressive types of MS, as well as those with relapsing disease who have not to date responded to any of the presently approved DMTs. Exciting new findings about the processes that underlay the development of MS and the mechanisms by which it produces nervous system damage are being made at an accelerated pace. The coming years should bring many promising advancements in the treatment of all types of MS.

As always, your personal healthcare professionals will be your best guides to making the right decision for you. The great news is that effective treatments are available for certain types of MS. If treatment is appropriate, as determined by your doctors, the keys to success are: (1) to start therapy early in the disease when it is the most effective in preventing the accumulation of nervous system damage; (2) to stay on therapy once you've begun; and (3) continue under the care of your medical team, to monitor your ongoing response to the disease-modifying therapy as well as any side effects.

Anyone interested in additional information about the clinical trials discussed here, or anyone interested in participating in a clinical trial, may visit **www.clinicaltrials.gov**. For more information about MS and its treatments, please contact MSAA at **(800) 532-7667**, or visit our website at **www.msassociation.org**. ◆

Ask the Doctor

by Dr. Jack Burks, Chief Medical Officer for MSAA

Due to limited space, this issue's *Ask the Doctor* column could not be included in this edition. Please visit our website to view this column online at **www.msassociation.org/publications/fall10/ask.asp**, or call **(800) 532-7667** to request a printed copy.

Chronic Cerebrospinal Venous Insufficiency (CCSVI) and MS

This Research Update would not be complete without mentioning the possible connection between chronic cerebrospinal venous insufficiency (CCSVI) and multiple sclerosis (MS). CCSVI is a complex condition involving changes in blood flow, which some researchers theorize could possibly lead to the activation of the immune system, excess iron deposits, loss of myelin, and other nervous system damage. With CCSVI, the veins located on the outside of the brain – those designed to transport blood from the brain back to the heart – collapse and/or become blocked, a condition known as **stenosis**.

Paolo Zamboni, MD from the University of Ferrara in Milan, Italy conducted some of the first studies with MS patients and CCSVI. He tested both healthy controls as well as 65 MS patients, and in April 2009, reported that all of the individuals with MS had CCSVI, versus none of the controls. More recent studies conducted by other researchers have not duplicated these results, but different diagnostic procedures could potentially affect the outcome. Zamboni also studied the effects of using an angioplasty type of procedure on these 65 individuals with MS, in an attempt to correct the CCSVI. For those whose veins did not close back up (**restenosis**), the results – in terms of reduced brain lesions and reduced relapses – were favorable.

On June 30, 2010, the University at Buffalo announced the PREMiSe (Prospective Randomized Endovascular therapy in Multiple Sclerosis) study to evaluate balloon angioplasty with CCSVI and its effects on MS. For more information, readers may visit **www.buffalo.edu** and search for CCSVI. Although the PREMiSe study is no longer recruiting participants, two other studies in Albany, New York may still be recruiting. For more information, visit **www.clinicaltrials.gov** and search for CCSVI.

While many CCSVI research proposals are presently under consideration, a number of individuals with MS have decided not to wait. Unfortunately, having the procedure performed outside of a clinical trial does pose risks and some adverse events have occurred. Larger and more rigorous studies are needed to confirm: (1) if CCSVI is involved with MS; (2) if the procedure to open these blood vessels is safe; (3) how to best perform the procedure; and (4) if the procedure will have a positive effect on MS-disease activity.

The opinion of many neurologists – including Dr. Zamboni – is that individuals with MS are strongly advised to either participate in a trial or wait until such studies are complete and the results are published before having the procedure performed. This will ensure greater safety and enable patients to make a more informed decision prior to undergoing this invasive treatment.

A QUICK OVERVIEW OF MS TERMINOLOGY

What are the common types of MS?
On average, 80 percent of people with MS begin with the **relapsing-remitting form of MS (RRMS)**. This type of MS has temporary symptom flare-ups (also known as "relapses" or "exacerbations"), followed by a complete or partial recovery ("remission"). If untreated, more than 90 percent of individuals with RRMS may eventually advance to **secondary-progressive MS (SPMS)**, within 25 years. This phase is reached when the patient experiences a progressive worsening of symptoms.

While approximately 80 percent of individuals with MS are initially diagnosed with RRMS, the majority of the other 20 percent are diagnosed with **primary-progressive MS (PPMS)**. This form of MS presents a gradual but steady accumulation of neurological problems from the onset, without the presence of relapses and remissions. Other types of MS exist, but these are less common.

Prior to a diagnosis of MS, individuals may be diagnosed with **clinically isolated syndrome (CIS)**. This is a single attack (or the appearance of one or more symptoms characteristic of MS) with a very high risk of developing MS.

What causes the symptoms of MS?
Nerve fibers (or **axons**) have a protective, fatty-rich protein covering known as myelin, which insulates the nerve fibers. MS is thought to be an **autoimmune disease**, where the body's immune system malfunctions by sending disease-fighting cells into **the central nervous system (CNS)** to destroy the body's own myelin. The CNS consists of the brain, optic nerves and spinal cord.

White blood cells, including **lymphocytes**, are produced when the immune system perceives a foreign body and instructs the cells to eliminate it. With MS, as these damaging immune-system cells circulate in the blood, they are able to breakthrough the protective **blood-brain barrier (BBB)** and enter the CNS.

Once the damaging cells enter the CNS, **inflammation** occurs in the areas where myelin becomes damaged and scarred. Areas of activity are known as **lesions** (or **plaques**). Ultimately, axons may become damaged as well. The flow of nerve impulses is interrupted along damaged areas of the myelin and nerve, causing the symptoms of MS.

What are some of the common tools used to evaluate MS activity?
Lesions may be viewed by a **magnetic resonance imaging (MRI)** scan of the brain and/or spine. **Inflammation** with these lesions can be better evaluated with **gadolinium-enhancement** – a type of dye given to the patient via injection prior to the procedure. A **lumbar puncture** (also known as a spinal tap) is a procedure where a very thin needle is inserted at the base of the spine and a small amount of **cerebrospinal fluid (CSF)** is collected. The neurologist will particularly be looking for **oligoclonal bands**, which are abnormal immune proteins called **immunoglobulins**.

Evoked potential (EP) tests measure the speed of the brain's response to visual, auditory (sound), or sensory (feeling) stimuli, using electrodes taped to the patient's head. Delayed responses can indicate possible damage to the nerve pathways. The **Kurtzke Expanded Disability Status Scale (EDSS)** uses whole and half numbers from one to 10 to measure degree of disability, largely in terms of mobility.

For a full explanation of MS terms, please visit www.msassociation.org/publications/summer07/health.asp

Cannonballs for Cash
JOSHUA WALTERS, Brownsburg, IN
to honor his aunt with MS
Funds Raised: **$1,035**

dive into ACTION

Swim for MS is a great way to incorporate your interest of swimming with your desire to help the MS community. Anyone with access to a pool can participate – plan your campaign around your schedule, your ability, and your preferred swim activity.

North Myrtle Beach Swim for MS
HALEY MIZELL, Little River, SC
to honor her grandmother with MS
Funds Raised: **$1,369**

Eight Days, 270 Laps
CINDY BOLTON, Phoenix, AZ
A lifeguard when diagnosed with MS, Cindy is still swimming strong!
Funds Raised: **$1,122**

SWIM FOR MS
ANY POOL, ANY TIME

MULTIPLE SCLEROSIS ASSOCIATION OF AMERICA

Register at
msassociation.org/swimforms

Program Notes

MSA to MSAA: Looking Back and Looking Forward

In looking back 40 years to the summer of 1970, the cost of a new home was $26,000, a gallon of gas was 36 cents, and a first-class stamp was just over a nickel. Also in 1970, Richard Nixon was president, America tuned in to see "Here's Lucy" and "The Mod Squad," while top hits included new releases from The Four Tops, Elvis Presley and The Partridge Family. Certainly times have changed! But what has not changed is MSAA's commitment to enriching the quality of life for everyone affected by multiple sclerosis.

Founded 40 years ago by a woman with multiple sclerosis and her husband in a small southern New Jersey community, the then-named "Multiple Sclerosis Association" (MSA) was an active, grassroots organization that provided direct services to local MS patients in the Philadelphia region. During the next two decades, MSA developed a highly successful core of services such as Equipment Distribution, a toll-free Helpline and public education programs.

As the need for these services grew, MSA expanded nationally and brought its unique brand of compassionate care and tangible services to many more MS patients across the country. In 1988, MSA incorporated "of America" into its name, reflecting this expansion. The organization now began delivering vital services to the MS community throughout the nation while increasing MS awareness, visibility and education.

MSAA marched into the 1990's, forging a historic partnership with the National Aeronautics and Space Administration (NASA). In working with NASA scientists and several prominent MS centers, MSAA helped advance the study of microclimate cooling and multiple sclerosis. These studies proved the positive effects of cooling on MS patients and ushered in a new national initiative for the organization: MSAA's Cooling Program.

As the world prepared to enter a new millennium, MSAA's board and staff also looked eagerly to the future and took significant strides to enhance the organization as a leader in the MS community. With the national expansion of its board of directors and a new executive management team led by current MSAA President and CEO Doug Franklin, MSAA refocused its efforts, expanded the size, scope and breadth of its programs and services nationwide, and embarked on its most successful period of its 40-year history.

The development of positive, working relationships with the leaders of the MS medical community, corporate partners and

fellow MS service organizations allowed MSAA to flourish during the 2000s. One of the many highlights is the creation and continuous expansion of the MRI Institute, a program that has assisted people with MS in acquiring nearly 4,000 MRI scans. Other highlights include the publication of numerous brochures, booklets and multiple issues of MSAA's magazine, *The Motivator*, along with the development of an extensive on-demand video library, and the creation of a comprehensive and easy-to-navigate website. MSAA's publications, video library and website have all been honored with top awards in the field of health-related communications.

Additional MSAA accomplishments include: the formation of new regional offices with increased localized services; a professional staff of Helpline consultants with a highly effective resource database to offer assistance; the distribution of tens of thousands of mobility, safety and cooling products; the expansion of the Lending Library, Networking and other programs introduced to better serve the MS community. All of these services have been provided free of charge through the generous donations of our loyal supporters and corporate partners.

Until a cure is found, we are very honored and proud to continue our mission of serving individuals with MS and their families. As we begin the next decade in this millennium, MSAA remains committed to reaching more people in more places than ever before through the expansion of technology, social media and other channels. We are also committed to developing additional programs and services that further enrich the quality of life for everyone affected by MS.

As always, thank you for the opportunity to serve you and allowing us to be a part of your life. To learn more about the full array of MSAA programs and services, please call **(800) 532-7667** or visit **www.msassociation.org**. ◆

- Robert Rapp and Peter Damiri

SURVEY PARTICIPANTS NEEDED

Individuals with a disability who work or volunteer needed to provide information about "Workplace Features that Aid Function"

The Rehabilitation Engineering Research Center on Workplace Accommodations (WorkRERC) at Georgia Tech is conducting a survey to examine the relationships between functional ability, job requirements, and the use of workplace accommodations. Workplace accommodations are technology, physical changes to the workplace, or policy changes that employees use to help them be more effective in their jobs.

You are eligible to take this survey if you have a disability or loss of function AND are employed or volunteer. The survey is anonymous and takes an average of 30 minutes to complete. You will have the option of saving your responses to continue the survey later if needed.

Please visit **www.surveygizmo.com/s/200473/workplace-features-that-aid-function** for more information and to access the survey. Individuals who prefer to take the survey by telephone may call **(404) 894-0561** to schedule a phone survey. Please pass this information along to others who may be interested.

Thoughts about Giving

The Meaning of Our Message

Another envelope!

As much as any development professional hates to admit it, we know "another envelope!" or "more mail!" are common reactions when donors receive the newest fundraising letter from MSAA or any charity.

One purpose of this column is to let donors know more about the fundraising process and to let donors in on the "trade secrets." This is in the hope that by understanding how and why MSAA and other charities operate, such knowledge will foster greater acceptance of practices that may have been confusing in the past.

Our messages are sent to inform you, to make you aware of all the good that your gifts are doing, and to make you proud to support an organization that accomplishes such good.

If MSAA could talk to every donor and find out exactly how he or she wanted to help or when he or she should be contacted, that would be great. In an imperfect world, that is not possible, so we have to do what we think is best for all concerned.

Historically, and to this day, MSAA receives the overwhelming majority of its support from individuals who generously make gifts by mail or via that other culprit, the telephone. These gifts have sustained MSAA and kept it operating without interruption for more than 40 years.

Why then do we send all of that mail? We write, we call, we send e-messages… we ask because we've learned that if you don't acquaint people with what you want, if you don't tell them how they can help, they won't know what to do for you or when to do it.

More commonly put: "If you don't ask, you don't get."

So we ask. There's nothing magical or mystical about it. Our donors are individuals whose gifts express their concern for the hundreds of thousands of people who face the unpredictable challenges of MS on a daily basis.

MSAA does, however, make a strong effort to not only ask, but to inform as well. We do not send the same formulaic letter or give the same telephone message each time. With each phone call or piece of mail you receive, we make a point of emphasizing our mission and how your kindness helps MSAA fulfill its mission. We tell you the stories of people we've served. We let you know how initiatives, such as our MSi online educational videos viewed by almost 30,000 people last year, help to enrich a constituent's quality of life.

While our messages are appeals, they are also records of important results we accomplished as partners. They are sent to inform you, make you aware of all the good that your gifts are doing, and to make you

proud to support an organization that accomplishes such good.

So the next time you see "another envelope," please open it and read it. It's bound to contain gratitude for all you do to help someone who has MS. The choice to make a gift at that moment is yours. The pride you'll receive from learning what your gifts have achieved is boundless.

SWIM FOR MS

Folks are diving in with unbridled enthusiasm to participate in MSAA's fun and easy fundraising program, "Swim for MS." Coast-to-coast, swimmers – individuals, groups of friends, or teams – are going to their local pools, suiting up, and doing laps in support of MSAA's programs and services. The Swim for MS slogan is "Any pool, any time!"

Swimmers ask friends, relatives, co-workers and others to make a gift to MSAA in honor of their effort to support people with MS, or in honor of a special person with MS. Some swimmers set goals and tell the stories that outline the reasons for a swim. These goals and stories may be viewed by visiting **support.msassociation.org/swimforms**.

We often email donors to let them know about a Swim for MS taking place in their community. It is gratifying when a neighbor who doesn't know the swimmer makes a donation on the swimmer's behalf, just to support the common cause of helping individuals with MS.

If you're interested in Swim for MS, please contact Malcolm Friend at MSAA by calling **(800) 532-7667, extension 117**. He may also be contacted via email at **mfriend@msassociation.org**.

CHARITABLE IRA ROLLOVERS

Several donors find themselves in an unusual situation as the new calendar year approaches. They have reached the age of 70 ½ and must take or transfer some funds from their tax-deferred IRA retirement accounts. The quandary comes when the person doesn't necessarily need or want to use the money.

One solution is to donate it to a charity. Until December 31, 2010, people can make an outright gift to MSAA using their IRA funds without tax implications.

While the donor cannot claim a charitable deduction for IRA gifts, he or she will not pay income tax on the donated amount as long as he or she transfers the funds directly to a public charity, such as MSAA. The gift generates neither a taxable income nor a tax deduction, so even people who do not itemize their tax returns can receive the benefit.

If you have questions about this type of donation, your financial advisor can give you more information. You may also discuss charitable IRA rollovers to MSAA with Neal Zoren, director of development at MSAA, by calling **(800) 532-7667, extension 128** or emailing **nzoren@msassociation.org**. ◆

- Neal Zoren
MSAA Director of Development

THE PHILANTHROPY CIRCLE

The following thoughtful corporations and foundations have contributed generously to MSAA to help enrich the quality of life for everyone affected by multiple sclerosis. Organizations providing gifts of $10,000 or more are shown in this listing.

GUARANTORS *($500,000 and up)*
EMD Serono, Inc. and Pfizer Inc
Teva Neuroscience

CHAMPIONS *($100,000 to 499,999)*
Acorda Therapeutics
Bayer HealthCare Pharmaceuticals
Bayer USA Foundation
Genentech Foundation
Novartis Pharmaceuticals Corporation

VISIONARIES *($50,000 to $99,999)*
Eli Lilly and Company
Genentech, Inc.
The Ronda Gruber Foundation

INNOVATORS *($25,000 to $49,999)*
Biogen Idec
IBM
Medtronic Foundation

ADVOCATES *($10,000 to $24,999)*
Avanir Pharmaceuticals
Catholic Human Services Foundation
The Chatlos Foundation
Grand Lodge Daughters of Scotia
The Horizon Foundation for New Jersey
The Wal-Mart Foundation

Volunteer with MSAA

Volunteering with MSAA offers you an opportunity to help the MS community by using your personal skills and expertise. Opportunities include:

Resource Detectives: MSAA needs you "on the case" as a Resource Detective™ to help identify valuable resources for the MS community. Use your skills to research and report information about local agencies and organizations that offer assistance to everyone affected by MS.

My Fundraising Idea: MSAA welcomes your creative ideas for special events directed to adults, teens, or children. Take the initiative and help MSAA reach its goals while having fun!

We seek your help today!

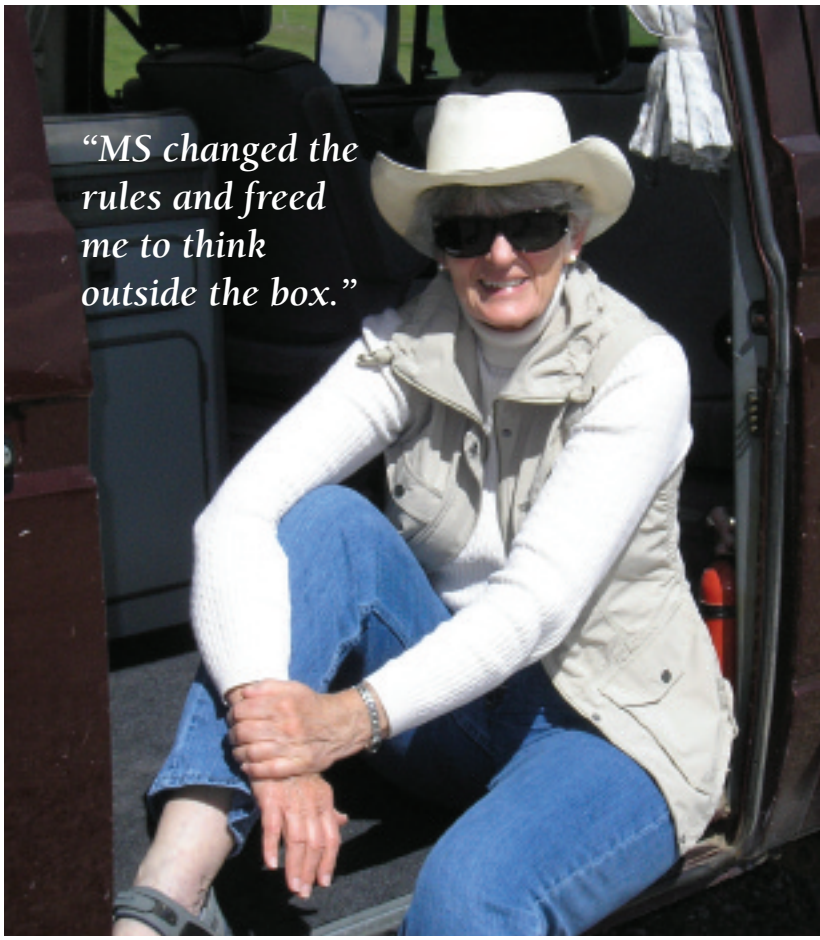
For more information, visit **support.msassociation.org/volunteer**, email **volunteer@msassociation.org**, or call **(800) 532-7667, extension 8**.

My Dream to Let Go and Fly

By Barbara Ellis

"If you want to hear God laugh, tell him about your plans."

-Woody Allen



I'm an adventurous woman. Twenty years ago my plans looked something like this: hike the Continental Divide Trail through Montana, canoe the Boundary Waters in Northern Minnesota, and explore Yellowstone National Park by horseback.

God laughed!

One of the challenges with MS is figuring out how to reinvent your life periodically. That doesn't mean you have to stop dreaming or give up who you are. It does mean seizing every moment that your body allows to do the things you love. Sometimes it requires thinking creatively, taking risks or experimenting with choices.

I was diagnosed with MS soon after my children left the nest. I had a satisfying career and was planning exciting things for my mid-life, when everything changed overnight. I felt like Alice-in-Wonderland plunging into the rabbit hole, unwittingly ratcheting down… down… down from a life as a busy healthcare executive to learning how to be a person with a disability, unable to work.

I wanted more than anything to find my way back to my old life. I grieved over the loss of my job and the challenge to my self-esteem. MS demands adjustment, sometimes many adjustments over and over again. I had difficulty adjusting to the lack of structure in my life, where previously I always had people-to-meet and places-to-go each day. I was, after all, an archetypical professional woman who planned her life and played by the rules.

Then one night I had a lucid, colorful dream. I was free-climbing a rugged vertical rock face slowly and confidently until I was within a few feet of safety near the top of the

wall. Suddenly, I found myself with no handholds in sight. My legs were stretched to the max and beginning to cramp. I was hundreds of feet off the ground without the smallest crack to reach for. I had no ropes to secure me and going back down was unthinkable. I was truly between a rock and a hard place.

As my dream continued, a relaxed voice spoke from the top of the cliff, "You are okay, but it's time for you to let go and fly. If you insist on hanging on, you will lose your grip, fall, and never learn that you've really always known how to fly – you were just afraid to try."

In this dream, I felt bone-chilling terror. My numb fingertips began to lose their grip and slip to the edge of the narrow crevices of the cold red sandstone. Again, in my dream, the voice spoke. "Use the strength you have left to let go. Push yourself away from the rock. Surrender to the unknown."

Adrenaline surged. My head pounded. My heart raced. ***I knew that I could not fly.*** Yet, as all of the energy ebbed from my fingers, I realized that I was grasping fiercely to control a situation over which I had no power. In my dream, I pushed myself away from the rock.

For a second or two I remained breathless, suspended in midair. Then, instead of plunging down as I'd anticipated, I lay prone on an invisible cushion of air and began to float. Cautiously, I spread my arms into the air and discovered that with minimal intent I could move in any direction. Anxiety subsided as I developed a delicate confidence.

The subtleties of flight began to feel instinctive. If I tried to force myself to go faster or make sharp turns, I lost buoyancy and teetered off balance. If, however, I allowed myself to relax and simply enjoy the experience on its own terms, I soared peacefully without struggle or tension. From this perspective, I could see that the success of my flight rested entirely on my willingness to abandon all previous notions of how my world worked. It had everything to do with acceptance and exploration of a new paradigm.

As I arose from the dream state, the clear distinction between the rock and my MS began to blur. The fear was gone and so was the voice; in their place was a sense of empowerment. ***It was time to surrender to the experience of discovering my new life… to let go and fly.***

But in real life, not in a dream, how does someone let go and fly? My third son, Rod, was the one who gave me the inspiration. At 23, he was the most adventurous and carefree of my four sons. Rod lived much of his adult life on a shoestring, traveling in an old Volkswagen bus, seeking mountains to climb and new rivers to kayak. Rod suggested that I, too, buy a Volkswagen bus in which to live and travel, so I could get the frequent rest I needed and still indulge in the travel and adventure that I'd always wanted to do.

At first, I thought I was too far into adulthood and a responsible work ethic to adopt his "no barriers" approach to life. Yet, his carefree spirit was an inspiration. MS changed the rules and freed me to think outside the box.

Thus, I became a vagabond. I lived and traveled like a turtle inside a six-by-15-foot shell on wheels while I regained strength and began to think about reinventing my life. My VW camper bus was the quintessential vehicle for hippies living on the road with no itinerary, agenda or timetable. But, I wasn't a hippie.

When I was strong enough to drive, I traveled to beautiful wild places where I could rest and recuperate. When I was weak, when my legs did not work or my hands and arms were unresponsive to the demands of the steering wheel, I would stop for the length of time it took to regain strength and function again before moving on.

I have been committed to a healthy lifestyle throughout adulthood and I believe it has helped me to live well with MS. However, the most powerful force in my life has been *the dream*. When I'm having a bad day from my MS or when I'm feeling down, I remember to "push myself away from the wall and enjoy the flight."

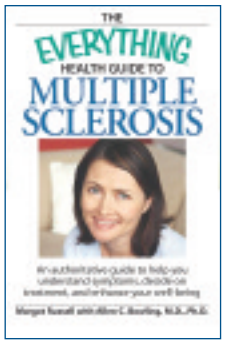
I had a birthday this June and celebrated by hiking the two-mile round trip to Bear Creek Falls in the Bitterroot Mountains near my home in Montana. No one could be more surprised than I to see I've made it this far or that I'm still walking the trails at age 70. Sure, MS has slowed me down and I trip a lot because my feet and legs are often numb, but hiking sticks are great inventions. Any day on a trail is better than the day after my diagnosis when it wasn't clear if I'd lost my ability to walk. So today, I treasure every step.

I still have my old VW van and my love of the outdoors. I no longer live in the van and I don't go exploring as much as I'd like, but I relish every new adventure. I know that between the realities of advancing age and MS, I will be reinventing myself for the rest of my life. Sometimes unexpected treasures are hidden within the difficult challenges in life, and sometimes, they may be found in our dreams. ◆

Barbara Ellis is a member of the patient advisory board of the CCSVI Alliance and is writing a book entitled, Eagle on the Highway: A Vagabond Journey of Adventure and Healing.

Barbara Ellis in her Volkswagen van, in which she lived and traveled to many beautiful places.

Spread the Word



The Everything Health Guide to Multiple Sclerosis: An authoritative guide to help you understand symptoms, decide on treatment, and enhance your well-being

Written by Margot Russell and Allen C. Bowling, MD, PhD

Published by Adams Media

MSAA Book #36

Written by a published author with MS and a well-known MS expert, this book seems to touch on almost "everything" concerning one's health and MS: from symptoms and treatments to alternative therapies, stress management and wellness strategies.

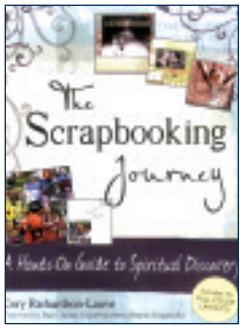
Multiple Sclerosis Manifesto: Action To Take, Principles To Live By

Written by Julie Stachowiak, PhD

Published by Demos Medical Publishing

MSAA Book # 35

This excellent resource covers a variety of important topics, including disease and symptom management, finding the best doctor for you, reforming relationships and preparing to enjoy life. This book is written by an epidemiologist (a doctor who specializes in the frequency, distribution and prevention of disease), who also has MS.



The Scrapbooking Journey: A Hands-on Guide to Spiritual Discovery

Written by Cory Richardson-Lauve

Published by SkyLight Paths Publishing

MSAA Book # 6

Author Cory Richardson-Lauve is an award-winning scrapbook designer. Described as inspirational and empowering, this book not only details the techniques for creating beautiful scrapbooks – for beginners and experts alike – but also looks at the spiritual side of gathering and artistically recording one's memories and aspirations.

MSAA Lending Library

To borrow books featured in this column or any other book in MSAA's Lending Library, please send us your name and address. We will send you an application and a list of books for the Lending Library. MSAA and its clients greatly appreciate any donations made to help build the Lending Library. If you would like to donate a book to the Lending Library you need only send it to us at the address below. Please address all correspondence to:

MSAA Lending Library
706 Haddonfield Road
Cherry Hill, NJ 08002

(Please reference book number)

2010 MSAA Art Showcase

Susan Glenn, *Untitled*
2009 Art Showcase

Submit Your Best Work!

*The theme of the **2010 MSAA Art Showcase** is "**Inspiration**." Please submit artwork that in some way might promote positive thoughts and emotions.*

Artwork will only be accepted from individuals who have MS. Submitted pieces must be two-dimensional; suggested mediums include: watercolor, acrylic, oil, pencil, pastel and ink. Sculpture, pottery, fabric and other types of three-dimensional works cannot be accepted. The art showcase will be displayed on MSAA's website during March 2011, in recognition of MS Awareness Month.

Submissions will be accepted between October 1 and December 15, 2010.

For submission guidelines, visit ***support.msassociation.org/artshowcase***

Paint tube image by Rachel Slepekis

For further information, contact:

Terry Dingle, Development Coordinator
MSAA
706 Haddonfield Road
Cherry Hill, NJ 08002
Email: tdingle@msassociation.org
Phone: (800) 532-7667, extension 146

Multiple Sclerosis Association of America
706 Haddonfield Road
Cherry Hill, NJ 08002 USA

CHANGE SERVICE REQUESTED

Make Your Wedding Day Memorable and Support MSAA

Honor a loved one on your special day…and help support MSAA.
Order your Wedding Favors at **support.msassociation.org/wedding**

- Give special meaning to your wedding day with a donation to MSAA, in place of conventional wedding favors.
- MSAA will provide you with personalized table tent cards, scrolls, or bookmarks.
- Customize the personalization of your favors once your donation is complete.

Photo generously donated by Tina from Pennsylvania

For more information, visit
support.msassociation.org/wedding
or call **(800) 532-7667, extension 117.**

"I just wanted to let you know that I received our wedding favors and they look wonderful. My mother found out about a year ago that she has MS and I cannot think of a better way than to honor her the day of our wedding. Thank you again!"

– Danielle I.

MSAA
Multiple Sclerosis Association of America

www.msassociation.org