MSAA
Summer/Fall 2011

# The Motivator

**Bringing Information to People with Multiple Sclerosis**

## MS RESEARCH UPDATE

An overview of approved and experimental treatments aimed at helping individuals with multiple sclerosis to feel their best


# ANY POOL, ANY TIME

## *Make a splash with Swim for MS ...any season of the year!*

**Swim for MS provides a unique volunteer fundraising opportunity that can turn a day at the pool into a meaningful way to help the MS community.**

**To learn more about this program and to see what other swimmers are planning, please visit msassociation.org/swimforms or call (800) 532-7667, extension 157**

SWIM FOR MS
ANY POOL, ANY TIME
MULTIPLE SCLEROSIS ASSOCIATION OF AMERICA

# My MS Manager™

## *MSAA's new mobile phone app, provided free of charge to help manage your MS and more!*

To learn more about this product and download from the iTunes store, visit **www.msassociation.org/mobile**

**QR CODE INSTRUCTIONS:**
QR-code enabled smartphone users may scan this image to download this app.

Available on the iPhone App Store

MSAA
MULTIPLE SCLEROSIS ASSOCIATION OF AMERICA


**Please note:** MSAA is *not* distributing free mobile phones. A mobile phone application (or "app") through the iTunes store is available as a free download to individuals with MS or their care partners to use on their iPhone, iPad, or iPod touch

The MOTIVATOR

Published by the Multiple Sclerosis Association of America



**MSAA National Headquarters**
706 Haddonfield Road
Cherry Hill, New Jersey 08002
**(800) 532-7667**
**www.msassociation.org**

*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

2010 National Health Information Awards Winner

2011 APEX Awards for Publication Excellence

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



COVER STORY

## *MS Research Update 2011*



This annual Research Update provides a comprehensive overview of the eight FDA-approved disease-modifying therapies used to slow MS activity as well as initial findings on many of the experimental treatments.

DEPARTMENTS



**WHAT'S THIS?**
QR-code enabled smartphone users may scan this image to view this issue of ***The Motivator*** on their mobile device.

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*

There has been a flurry of activity at MSAA starting with the launch of our first mobile phone application, *My MS Manager*™, as well as our S.E.A.R.C.H.™ initiative to assist the MS community with learning about treatment choices. We participated in both the American Academy of Neurology (AAN) and the Consortium of Multiple Sclerosis Centers (CMSC) annual meetings earlier this year, which provided a wealth of information. We are pleased to summarize the key highlights in our annual "Research Update" appearing in this issue.

Our recent collaboration with the National Multiple Sclerosis Society (NMSS) on an article discussing the needs of the primary-progressive multiple sclerosis (PPMS) population was published in the Summer 2011 issue of the *International Journal of MS Care*. Please visit the Recent News section of MSAA's website (at **www.msassociation.org**) to read the article.

Currently, we are working in partnership with the National Disability Institute (NDI) to better understand and address the financial needs of the MS community. Together, MSAA and NDI have created an online survey as well as focus groups to evaluate needs and help design a specific financial education program. The input gathered has been used to create a webinar series; please see the inside back cover of this issue for details.

We continue to be inspired by our many volunteers, such as Rebecca and Jarrod Schlenker. The brother-and-sister team from Cranford, New Jersey, formed "Jabeccawalk: End to End for MS," a 2,181-mile hike along the Appalachian Trail. Over the course of four months, the duo trekked from Georgia to Maine, raising funds in support of MSAA's mission. You may read about their adventures at **jabeccawalk.blogspot.com**.

I encourage everyone to visit **www.msassociation.org** and select "Volunteer" to see how you can help support MSAA's vital mission. Don't forget about our Swim for MS program – Any Pool, Any Time makes it easy to volunteer for MSAA, no matter what the season! ◆

*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.*

NEW

# COPAXONE CO-PAY solutions™

Tricia C., on COPAXONE®
since 1999.

**NO MORE THAN $35 PER MONTH***

Whether you're already on COPAXONE® or just starting—now most people with insurance will pay no more than $35 per month out of pocket.*

## Your co-pay could be lower. Call **Shared Solutions®** today! **1-800-887-8100**

*Certain limits and restrictions apply.

Terms and Conditions: COPAXONE Co-pay Solutions™ is open to both new and existing patients who are residents of the US or Puerto Rico and who have private insurance coverage. The offer is not valid for patients covered in whole or in part by Medicaid, Medicare, TRICARE, or any other federal or state government pharmaceutical assistance plan or program (regardless of whether a specific prescription is covered), or by private health benefit programs that reimburse for the entire cost of prescription drugs. Use of this offer must be consistent with the terms of any drug benefit provided by a health insurer, health plan, or private third-party payor. This offer is void in Massachusetts or where otherwise prohibited by law, taxed, or restricted. No additional purchase is required. This offer is valid only at participating pharmacies and may be changed or discontinued at any time without notice. This program is not health insurance.



TEVA Neuroscience

shared solutions®
support. knowledge. answers.

COPAXONE®
(glatiramer acetate injection)
www.copaxone.com

# MS RESEARCH UPDATE

ON CURRENT AND EMERGING THERAPIES 2011

A comprehensive overview of the eight FDA-approved disease-modifying therapies used to slow MS activity, along with initial findings on many experimental treatments

**Written by Diana M. Schneider, PhD**
**Reviewed by Jack Burks, MD**
**Edited by Susan Wells Courtney**

Based on the positive response to the MS Research Updates published from 2007 through 2010 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 long-term treatment of MS. Highlights and recent research results are provided for each drug. This is not a complete list and not all study results are included. Initial study results should be considered as preliminary, since 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 conferences hosted by the American Academy of Neurology (AAN), the Consortium of Multiple Sclerosis Centers (CMSC), and the American and European Committees for Treatment and Research in Multiple Sclerosis (ACTRIMS and ECTRIMS).

**IN THIS SECTION**



Currently available medications continue to show effectiveness over the long term. A 2011 review by Mark S. Freedman, MD, in the journal *Neurology*, summarized the positive long-term data for Avonex®, Betaseron®, Extavia®, Rebif®, and Copaxone®. These drugs reduce the frequency and severity of relapses. They also show that long-term treatment improves outcomes by delaying the time to significant disease progression. In addition, treatment begun early in the disease process is correlated with optimal outcomes over the long term.

Preferably, treatment is now often started when a person is diagnosed as having a clinically isolated syndrome, or 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. With today's MRI technology, it is no longer considered necessary to wait for a diagnosis of MS as "disseminated in space and time." This was a diagnosis made on clinical grounds alone, and

required waiting until at least a second attack occurred before beginning treatment. The MRI findings can now be used as an adjunct to the clinical evaluation.

Recent studies with Tysabri® indicate that the drug may achieve a sustained improvement in disability for individuals with relapsing-remitting MS (RRMS). It substantially reduces clinical and MRI activity when other therapies fail. Progressive Multifocal Leukoencephalopathy (PML), an often-fatal viral infection of the brain, continues to be a concern. However, early diagnosis and treatment increases the survival rate to 80 percent (although often with disability). A blood test to determine those at greatest risk is currently under review by the Food and Drug Administration (FDA).

In September 2010, Gilenya® (fingolimod) became the first oral DMT approved by the FDA for the treatment of relapsing forms of MS. Studies show that it reduces disease activity and the progression of disability, while offering the advantages of an oral medication to individuals who have difficulty with the injected DMTs. Particularly when starting this treatment, and at regular intervals afterwards, patients are monitored for potential adverse events.

During the coming year, we anticipate that other new oral medications will be submitted for evaluation and potential approval by the FDA, including teriflunomide, laquinimod, and dimethyl fumarate (BG-12). One new injectible, Lemtrada® (alemtuzumab, formerly known as Campath and given via intravenous injection), may also enter or complete the approval process. Several more injectible drugs are also on the horizon, such as ocrelizumab, daclizumab, and Tovaxin®.

**Please note that all articles noted below appeared in previous issues of *The Motivator* and may be easily accessed through MSAA's website at www.msassociation.org by selecting "Publications," "*The Motivator,*" and the year for the issue.**

A brief overview of MS terms and clinical trials is on page 38 of the Summer/Fall 2010 issue of *The Motivator*. For additional information, the "Health and Wellness" column from the Summer 2007 issue of *The Motivator* gives an overview of MS terminology, evaluative procedures, clinical trials, and treatments.

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."

For more information (and earlier study results) on the approved and experimental drugs discussed in this article, please see previous "Research Updates" appearing in earlier Summer issues of *The Motivator,* from 2007 through 2010.

Please note that this article does not include medications for managing the symptoms of MS. Treatments for symptom management are the subject of the cover story in the Winter/Spring 2009 issue of *The Motivator*.

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.

## Avonex® (interferon beta-1a)

**Company:** Biogen Idec

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

The FDA approved Avonex in 1996 for relapsing MS and more recently for individuals with clinically isolated syndrome (CIS).

Avonex has been shown to reduce the number of relapses and lesions on MRI, as well as slowing 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 inflammation. They also prevent the transport of damaging lymphocytes into the brain. Lymphocytes are immune-system cells produced to fight infection and disease.

The ASSURANCE study includes 15-year data and shows that early suppression of clinical disease activity by Avonex is a marker of treatment response. This is associated with significant long-term benefits for quality of life as compared to patients who had received placebo. These results support other accumulating evidence that short-term responders to Avonex also experience beneficial long-term outcomes.

A 10-year analysis of data from the CHAMPS trial, which treated patients with CIS and a positive MRI, showed that although some had characteristics of disease progression, there was evidence of improved disease course with early treatment. These results emphasize the value of early treatment. This effect remained evident in both the CHAMPIONS five- and 10-year extension studies.

The Phase III clinical trial (ADVANCE) continues to enroll patients with relapsing-remitting MS (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 (Avonex) molecule that allows it to be given subcutaneously (under the skin) every two or four weeks, in contrast to the current once-a-week, deeper, 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.

Of approximately 1,260 ADVANCE participants, up to 120 will also be enrolled in a sub-study that will involve optical coherence tomography (OCT). This is a rapid, noninvasive, office-based imaging technique that allows objective evaluation of the thickness of the retinal axon (the nerve behind the eye) and nerve layers that atrophy (shrinking due to nerve cell death) in MS. Preliminary evidence supports the use of OCT as an objective tool to monitor the effectiveness of therapy, and it is hoped that OCT may be used as an outcome measure in future studies.

**Combination and Comparative Studies:**
The ongoing Phase III CombiRx trial for RRMS is comparing three treatment arms: Avonex with Copaxone, Avonex alone, and Copaxone alone. The study has 1,008 participants; it began in 2005 and is scheduled for completion in July of 2012.

## Betaseron® (interferon beta-1b)

**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 inflammation. They also prevent the transport of damaging lymphocytes into the brain. Lymphocytes are immune-system cells produced to fight infection and disease.

Follow-up data after 21 years from Betaseron's initial Phase III trial of RRMS show continued effectiveness and safety, as well as increased longevity. The results suggest that treatment was more effective when given early in the course of the disease, and a more favorable outcome can be seen for those patients who received the active drug in the very first trials, when compared to those who initially received placebo and could later switch to any disease-modifying therapy.

Improved effects of early treatment were also demonstrated in a group of 468 patients with CIS who were randomized to active treatment or placebo. By five years, the treated group showed greater improvement in scores on the Paced Auditory Serial Addition Test (PASAT), a measure of cognitive function.

The small SMART study of 25 patients with RRMS was designed to identify immune markers of Betaseron therapy. Immune markers are tendencies or indicators that are observed across a population with a particular disease state. Immune markers in this study were compared in those patients with and without relapses during the first year of treatment.

Data from the study have now been analyzed, and the treated group showed significant changes in the levels of several immune-system markers. Twelve relapses occurred in 11 patients. A trend toward higher levels in the pro-inflammatory cytokine interleukin-17 (IL-17) was found in the relapsing group. Cytokines are small proteins that may stimulate or inhibit the function of other cells. Higher brain-derived neurotrophic factor (BDNF) levels were observed in the relapse-free group. BDNF is a protein found in the brain that helps to support nerves and their development.

The data suggest that the mode of action of the beta interferons may involve a shift in cytokines in favor of an anti-inflammatory/regulatory profile. Findings also suggest that elevated IL-17 may correlate with having relapses, while increased levels of another cytokine, BDNF, may be protective. These findings serve as a platform for further research of biomarkers predictive of responses to interferon therapy.

CORRECTION: Our previous issue had an error in Dr. Sadovnick's title on page 4. It should read: Director, MS Society of Canada endMS Western Pacific Regional Research and Training Centre. We apologize for the error.

## Extavia® (interferon beta-1b)

**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 may also vary. The latest information is available through the patient-support programs at these two companies. For more information, visit **www.msassociation.org**, and select "About MS," and "Sources of Information."

## 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.

## Rebif® (interferon beta-1a)

**Company:** EMD Merck 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 44 mcg 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 has also 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 inflammation. They also prevent the transport of damaging lymphocytes into the brain. Lymphocytes are immune-system cells produced to fight infection and disease.

The REFLEX study of 517 patients is comparing the efficacy of two dosing frequencies (once or three times per week) of Rebif versus placebo. The effect studied is the conversion to definite MS in patients with clinically isolated syndrome (CIS), which is also referred to as a "first demyelinating event." The primary endpoint was the time to confirmed MS using the McDonald criteria, which is a set of guidelines used to confirm a diagnosis of MS. The secondary endpoint was time to clinically definite MS (CDMS). Rebif significantly delayed development of MS as compared with placebo. This conversion was more pronounced with the higher dose (44 mcg three times weekly).

The Phase IV SKORE study continues to evaluate 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 include the proportion of relapse-free subjects and the proportion with defined EDSS changes. "EDSS" refers to the Kurtzke Expanded Disability Status Scale, which uses numbers from one to 10 to measure degree of disability, largely in terms of mobility. The study has 300 participants; it was initiated in June 2009 and is scheduled for completion in November 2013.

A Phase IV observational study is ongoing but is not recruiting participants. It is evaluating the effectiveness of Rebif therapy on quality of life, using two health-related, quality-of-life measures.

A multi-center, observational, 96-week Phase IV study is evaluating whether the use of the RebiSmart™ self-injection system improves compliance with Rebif in subjects with relapsing forms of multiple sclerosis.

*A German study looked at the effects of interferons and Copaxone on pregnancy and relapse rate. This study re-confirmed the reduced MS relapse rate during pregnancy and the increased relapse rate after birth. Exclusive breastfeeding seemed to have beneficial effects on postpartum relapse-rate reduction. While these data also support previous findings that the interferons and Copaxone do not present a major risk for birth defects, anyone who is pregnant or plans on becoming pregnant should discuss the risks and the benefits with her doctor before starting or continuing any disease-modifying therapy.*

## Copaxone® (glatiramer acetate)

**Company:** Teva Neuroscience, Inc.

Given through daily subcutaneous injections; dosage is 20 mg.

Approved for RRMS and CIS.

Copaxone has been shown to significantly reduce the annual relapse rate in RRMS and reduce the risk of people with CIS 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 (the protective covering of the nerves) that is damaged in MS. This therapy appears to decrease immune-system T cells that damage myelin, and may decrease inflammation by favorably shifting the balance among T-cell subtypes as well as by affecting several interleukins. (Interleukins are a type of cytokine, which are small proteins that may stimulate or inhibit the function of other cells.) Copaxone may also induce lymphocytes (immune-system cells produced to fight infection and disease) to produce factors that enhance the survival of cells that produce myelin, and may have a neuroprotective action that prevents damage to axons (nerve fibers).

An international European study was conducted to determine whether immediate treatment with Copaxone is better than delayed treatment in preventing conversion to clinically definite MS (CDMS). This study has shown that, over five years, early treatment with Copaxone reduced the risk of converting to CDMS by 41 percent. These results establish the importance of initiating treatment with Copaxone as early as possible to protect patients from the accumulation of disease activity.

Primary-relapsing MS (PRMS) is the least common form of MS. This has a disease onset of gradual worsening with subsequent relapses. There has been some debate as to whether it is justified to categorize PRMS separately from primary-progressive MS (PPMS) in terms of clinical course and prognosis. A sub-analysis of the PROMISE study of 943 patients with PPMS (which failed to show that Copaxone was effective in this group), evaluated differences in baseline characteristics and disability progression between patients with PPMS and PRMS. It showed that some PPMS patients will ultimately convert to PRMS. Although the numbers of PRMS patients analyzed in this study were small, the results suggested that disease progression is more rapid in this clinical sub-group.

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

A Phase II trial to study the effect of combining Copaxone and estriol (a naturally-occurring estrogen hormone) in RRMS on relapse rate is continuing. 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, more definitive trial that might lead to a new oral treatment option for women with MS. A pilot trial was encouraging.

# My shoes look forward to taking a walk

**AMPYRA®** (dalfampridine) is indicated as a treatment to improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed.

**AMPYRA is an oral tablet, not an infusion or injection**

**AMPYRA can be used in any of the four major types of MS**

**AMPYRA can be taken alone or with other MS medications**

**AMPYRA improved walking in significantly more people than placebo in 2 clinical trials (34.8% vs. 8.3% and 42.9% vs. 9.3%)**

AMPYRA does not work for everyone.
Please talk to your doctor to see if AMPYRA is right for you.

**MoreAboutAmpyra.com**
**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 right 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.

This is not the full safety information. For more information, please refer to the Medication Guide on the next page. 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.*

ACORDA® THERAPEUTICS



AMP752D

## 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.*



1010427ATH-0

ACORDA® THERAPEUTICS

## Gilenya™ (fingolimod, FTY720)

**Company:** Novartis Pharmaceuticals Corp.

Oral medication; 0.5 mg capsule taken once daily.

Approved for relapsing forms of MS.

Gilenya (pronounced as "Jil-EN-ee-ah") is the first in a new class of immunomodulatory drugs, called "S1P-receptor modulators." It is similar in structure to a naturally occurring component of cell-surface receptors on white blood cells. (White blood cells are produced by the immune system to fight infection and disease.) Gilenya blocks potentially damaging T cells from leaving lymph nodes, lowering their number in the blood and tissues. It may reduce damage to the central nervous system (CNS) and enhance the repair of damaged nerves. The CNS consists of the brain, optic nerves, and spinal cord. Study data suggest that Gilenya may have neuro-protective effects.

Some adverse events with Gilenya include: an initial reduction in heart rate; infrequent transient AV conduction block of the heart; macular edema (a condition that can affect vision, caused by swelling behind the eye); and infections, including herpes.

### Study Information (we refer you to our 2010 Research Update for more details):

The FREEDOMS Phase III study of the (now FDA-approved) low-dose (0.5 mg) versus high-dose (1.25 mg) Gilenya and placebo showed the drug to be safe and well tolerated. Gilenya reduced the risk of confirmed disability progression by 30 to 32 percent versus placebo, and significantly increased the proportion of patients who were disease-free over two years. It also resulted in a 30-percent reduction of brain volume loss as compared with placebo at one and two years, suggesting a possible direct neuroprotective effect.

A Phase III extension study, FREEDOMS II, evaluated long-term safety, tolerability, and efficacy; all 1,080 participants received Gilenya. Its safety has now been tested in more than 2,600 patients. More than 10,000 patients in the United States have begun therapy with Gilenya.

Two deaths from herpes virus infections occurred in the FREEDOMS trials; both of these individuals received a higher dose of Gilenya, which is not FDA-approved or prescribed. No deaths were reported in those individuals treated with the FDA-approved lower dose, the only dose available for MS patients.

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 compared to weekly intramuscular injections of Avonex in individuals with RRMS. In summary, Gilenya was more effective in reducing the annual relapse rate, 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. No difference in progression of disability was demonstrated in this 12-month study.

In both the FREEDOMS and TRANSFORMS studies, Gilenya significantly reduced the

## Gilenya (continued)

frequency of severe relapses and those that required intervention (steroids or hospitalization), and reduced the number of relapses with no or partial recovery. It also consistently reduced the annualized relapse rate in patients with highly active MS as compared to Avonex.

The 36-month INFORMS study in 940 individuals will evaluate the effect of Gilenya relative to placebo on delaying the time to sustained disability progression in patients with PPMS. It will also evaluate safety, tolerability, and the effects on MRI parameters.

The six-month Phase IV EPOC study is currently recruiting participants. It will evaluate patient-reported outcomes, physician assessment of a change, as well as safety and tolerability in patients with relapsing MS who had previously been treated with other DMTs and are now receiving Gilenya. These outcomes will be compared to those who continue to receive one of the other approved DMTs. The study will have approximately 1,000 participants and is scheduled for completion in June 2012.

A long-term study of approximately 1,200 people with the relapsing forms of MS began in February 2011 and is scheduled to terminate in February 2019. The study will collect long-term data on safety and effectiveness.

# How to S.E.A.R.C.H.™ for the Right MS Therapy for You!


Multiple sclerosis is an ever-changing landscape. With eight treatments available and more on the horizon, how do you decide which is the right MS therapy for you?

Much like a GPS system, MSAA has developed the S.E.A.R.C.H.™ tool to help you and your physician navigate through the ever-changing MS landscape and reach your desired destination.

Each letter represents the key areas that should be considered when searching for the most appropriate MS treatment. S.E.A.R.C.H.™ stands for **Safety; Effectiveness; Affordability; Risks; Convenience; and Health Outcomes**.

*This program is made possible through unrestricted educational grants from Bayer HealthCare Pharmaceuticals, Biogen Idec, and Teva Neuroscience.*

To learn more about S.E.A.R.C.H.™ – including a downloadable patient workbook, treatment chart, resource guide, and a reference card, call **(800) 532-7667** or visit **www.msassociation.org**.

## Tysabri® (natalizumab)

**Company:** Biogen Idec and Elan Pharmaceuticals, Inc.

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

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

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

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 the EDSS were stable or improved in 59 percent of patients.

### Study Information:

The Phase III SURPASS trial continues to evaluate 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.

A small Phase II clinical trial, Natalizumab Treatment of Progressive Multiple Sclerosis (NAPMS), is continuing at Copenhagen University Hospital to study the safety and efficacy of Tysabri treatment of PPMS and secondary-progressive MS (SPMS). It enrolled 24 patients and is scheduled for completion in January 2012.

A small study of 20 individuals with RRMS is evaluating the role of Tysabri on cognition and neurodegeneration (the breakdown or cell death of nerve cells). Its objective is to further establish the role of Tysabri in preventing neurodegeneration in MS and to establish new markers for such damage.

A small Phase IV study of 20 individuals who have been treated with Tysabri for 12 months, is gradually switching Tysabri treatment to Betaseron and comparing it to continuing treatment with Tysabri. The primary outcome measure is the time to a first relapse during the study; other measures include clinical and MRI findings, as well as patient-reported outcomes on quality of life and fatigue. Safety will be assessed by reports of adverse events.

Other studies are exploring the effects of Tysabri on ambulation (walking and mobility), cognition, fatigue, depression, bladder function, sexual function, disability, and health-related quality of life. One study indicated that Tysabri-treated patients had fewer MS-related hospitalizations and emergency-room visits over one year of treatment, suggesting that it may reduce the economic burden of MS.

## Tysabri (continued)

### Progressive Multifocal Leukoencephalopathy

Following a suspension of the drug in 2005 after two patients developed Progressive Multifocal Leukoencephalopathy (PML), an often-fatal viral infection of the brain, Tysabri was re-released in 2006. While often fatal, when discovered early in patients taking Tysabri, new treatments have helped many to survive this infection by removing Tysabri from the blood system. Severe disability is still a major concern. All patients now receive the drug through safety monitoring programs.

As of September 2011, there were 150 reported cases of PML with Tysabri, and its labeling has been updated to further quantify the risk. The new labeling also notes the increased risk from previous use of immunosuppressive medications.

The three major risk factors for developing PML are: being on the drug for more than two years; prior immunosuppressant therapy; and positive blood tests for previous infection with the JC virus, which causes PML.

It is presumed that patients with no antibodies to the JC virus will be at a much-reduced risk of developing PML. A new assay (a test used for analysis) has been developed to identify antibody-negative patients. This JC virus antibody blood test is now commercially available and is under review by the FDA.

The JCV Antibody Program (STRATIFY-2) began April 2010 and is scheduled to end December 2012. It will enroll 8,000 participants. This program will define the prevalence of the JCV antibody in the MS population, and potentially stratify patients into lower or higher risk for developing PML based on antibody status.

## Novantrone® (mitoxantrone)

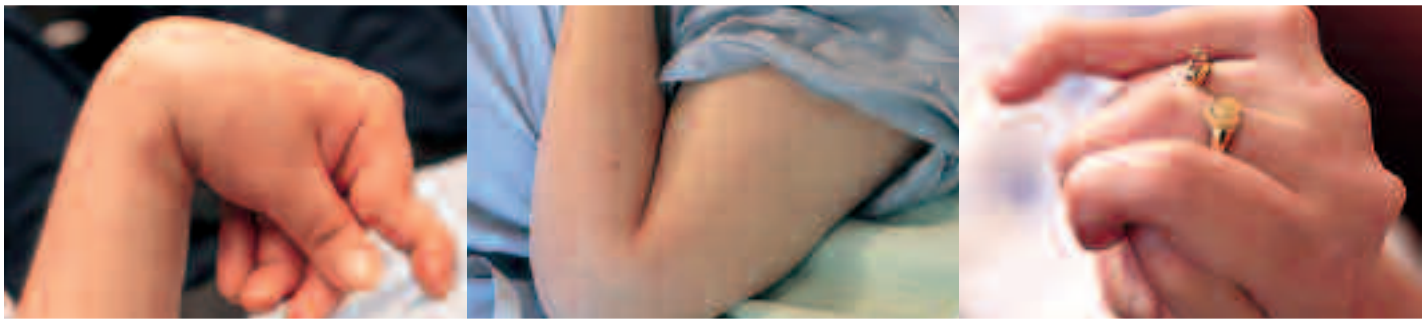
**Company:** EMD Serono, Inc.

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 is limited to avoid risking damage to the heart.

Novantrone is approved for use in SPMS, 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, reduce the number of relapses, delay the time to disability progression, and decrease 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 many 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. The risk of leukemia and cardiotoxicity have dramatically reduced the use of Novantrone in the United States.



I wish I could learn more about spasticity.

I wish there were tips for caregivers.

I wish I could find the support I need.

I wish I understood my treatment options.

I wish I was more prepared to talk to my doctor.

I wish I could hear from others living with spasticity.

**I wish there was more information about what to expect.**

*Explore your wishes at*

# LookForSpasticityAnswers.com

**LookForSpasticityAnswers.com** is dedicated to educating people affected by spasticity about the condition and its treatment options.

I:wish

***Create*** your ***Wish List Discussion Guide*** to help prepare to talk to your doctor.

**Find out** about spasticity • **Learn** about treatment options
**Read** stories from people living with spasticity • **Get information** for caregivers and more!



Spasticity A:nswers

# Cladribine

**Company:** Merck Serono, Inc.

The FDA gave Fast Track approval status to cladribine in July 2006. In March 2011, the FDA announced that it would not approve oral cladribine for MS without more safety information. In June 2011, Merck Serono announced that they will not currently pursue global approval for Cladribine Tablets for the treatment of RRMS, but would continue existing clinical trials. The company may consider a reapplication if safety concerns are lessened.

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

This drug predominantly affects peripheral blood lymphocytes (immune-system cells produced to fight infection and disease), 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.) Cladribine also seems to directly influence the overall T-cell response, which is believed to play a major role in the MS process.

The two-year Phase III CLARITY trial of two levels of cladribine versus placebo involved 1,326 patients with RRMS. Each course consisted of once-daily administration for four-to-five consecutive days, and study patients 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 and 31-to-33-percent reductions in disability progression, as well as 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 are receiving cladribine; it will continue to assess safety, tolerability, and effect on progression of disability. Studies have shown a high compliance and study completion with few adverse event-related discontinuations.

The long-term safety of cladribine is being tested in the eight-year PREMIERE registry, designed to provide long-term safety and risk-benefit information in approximately 1,500 patients who participated in other cladribine clinical trials. The study is scheduled for completion in 2018.

The ONWARD Phase II study of 200 individuals who have experienced at least one relapse while taking Rebif is ongoing. This study combines oral cladribine with Rebif, to determine whether the combination is more effective than Rebif alone. It has an estimated completion date of November 2013.

The Phase III ORACLE MS study is ongoing. It 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, also referred to as clinically isolated syndrome (CIS).

The risk for adverse events with cladribine includes the potential for developing infections, with herpes being the most common. A prolonged decrease in white blood cells has also been seen in some patients.

## BG-12 (dimethyl fumerate)

**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 anti-inflammatory cytokines (small proteins that may stimulate or inhibit the function of other cells) and appears to suppress damaging macrophage cell 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 initially being studied in RRMS.

The Phase III DEFINE study, which compared two doses of BG-12 against placebo in 1,200 patients, was completed in February 2011. After two years of treatment, BG-12 reduced relapses by 49 percent, and decreased the rate of disability progression by 38 percent.

The Phase III CONFIRM study, completed in September 2011, tested two dose levels against Copaxone and placebo in 1,232 patients. The primary measure was a reduction in relapse rate.

A Phase III continuation study of 1,700 patients who participated in the DEFINE and CONFIRM studies will evaluate the long-term safety profile of BG-12 as well as its long-term efficacy on clinical outcomes, MRI scans, and quality-of-life. The study will be completed in June 2013.

The Phase II EXPLORE trial is evaluating 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 in combination with interferons or Copaxone to 100 people (who continue to have evidence of disease activity despite receiving consistent monotherapy for at least one year). Efficacy endpoints will also be assessed in a subset of participants. The study began in May 2010 and will be completed in October 2011.

Trials to date indicate that BG-12 is safe and that its overall tolerability improves with continued use. Side effects include skin flushing and gastrointestinal symptoms.

## Laquinimod

**Company:** Teva Neuroscience, Inc. and Active Biotech

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

Laquinimod is being studied in RRMS. Although its exact mechanisms of action are unknown, it is an immunomodulator, apparently through its effects on cytokines and interleukins. It enhances T-regulatory cell activity, which reduces Th1-inflammatory T-cell activity. It also appears to reduce white blood cell penetration of the central nervous system (CNS).

In addition to its immunomodulatory actions, laquinimod increases levels of the brain-derived neurotrophic factor (BDNF), possibly contributing to neuroprotection in MS patients. BDNF is a protein found in the brain that helps to support nerves and their development. It also appears to prompt a neuroprotective response from cells within the CNS.

The Phase III ALLEGRO study of 1,106 individuals with RRMS has been completed. Compared to placebo, laquinimod reduced the annualized relapse rate by 23 percent and the progression of disability by 36 percent. It also reduced T1-hyperintense lesions by 27 percent, new gadolinium-enhancing lesions by 37 percent, new T2 lesions by 30 percent, and brain atrophy by 33 percent.

The BRAVO Phase III trial is a global, 24-month, double-blind study with 1,300 participants designed to evaluate laquinimod's efficacy, safety, and tolerability versus placebo. It will also provide risk-benefit data for laquinimod versus Avonex. Outcome measures are relapse rate, accumulation of disability, and disease activity on MRI. In August 2011, the sponsors announced that the study had failed to achieve its primary goal of reducing the annualized relapse rate, although there may be a trend in that direction if a subset of the data is adjusted for differences in MRI characteristics at the start of the study. Further analysis is ongoing.

A three-year Phase III study of 1,332 individuals with RRMS who completed the BRAVO study is scheduled for completion in June 2013. It will evaluate laquinimod's long-term safety, tolerability, and effect on disease course.

## Statins

Statins are oral medications that are most commonly prescribed to lower cholesterol. Current interest is based on a non-controlled observational study (a study without a control group) suggesting that the risk of developing new brain lesions was reduced by about half if patients with early forms of MS were taking atorvastatin (Lipitor®). However, a three-year Danish study of patients with RRMS failed to find any beneficial effect for simvastatin as an add-on therapy to Avonex. (The use of statins to lower cholesterol in patients on interferons should be discussed with a healthcare professional to consider the potential benefits versus risks.)

## Teriflunomide

**Company:** Sanofi

Oral medication taken daily.

This drug is an immunomodulator that affects the production of T and B cells. It inhibits rapidly dividing cells, including activated T cells, which are thought to drive the disease process in MS. It may inhibit nerve degeneration by reducing the production of free radicals, possibly decreasing the risk of infections and other complications linked to chemotherapy-like drugs.

The TEMSO trial for RRMS compared 7 and 14 mg of teriflunomide in 1,088 individuals. Both doses significantly reduced the annualized relapse rate by approximately 31 percent. Teriflunomide (7-mg dose) resulted in a 39.4- percent reduction in brain lesion volume on MRI compared with placebo; the 14-mg dose resulted in a 67.4-percent reduction. The 14-mg dose also reduced the risk of sustained disability progression by 29.8 percent relative to placebo. The number of gadolinium-enhancing lesions were also reduced with both doses compared with placebo, and there was a trend toward a greater effect with the higher dose.

A Phase III extension study of TEMSO is now underway. Patients who completed the original study and who received the drug are being maintained on the same dose; those who received placebo are randomized to teriflunomide 7 mg or 14 mg. The study remains double-blinded.

The TOWER efficacy study of 1,110 individuals with RRMS is scheduled from August 2008 to February 2013. It will test 7-mg and 14-mg doses versus placebo. Its primary endpoint is the annualized relapse rate; the secondary endpoint is time to disability progression. Results of this second of two placebo-controlled Phase III trials, which are required to support an application for regulatory approval, are expected in 2012.

The ongoing Phase III TOPIC study of 780 individuals with clinically isolated syndrome (CIS) is scheduled from February 2008 to November 2015; it is still recruiting participants. It also is comparing 7- and 14-mg teriflunomide versus placebo. The study's primary endpoint is the time to conversion to clinically-definite MS after CIS. Several secondary endpoints include: MRI findings; relapse rate; disability and progression. The drug's safety will also be evaluated.

The TENERE Phase III study is comparing 7- and 14-mg teriflunomide with Rebif in 300 people. It is scheduled from April 2009 to July 2012.

Following a Phase II study indicating that combined treatment with teriflunomide appears to be superior to an interferon given alone, the TERACLES Phase III study began in January 2011 and is scheduled for completion in April 2014; it is currently recruiting 1,455 participants. The study will compare relapse rates while taking a 7- or 14-mg dose of teriflunomide or placebo, in combination with an existing interferon treatment. The primary outcome measure is the annualized relapse rate. Secondary outcome measures include: MRI findings; disability progression; time to a first confirmed relapse; and the proportion of patients who are relapse-free.

# ABOUT MONOCLONAL ANTIBODIES

Monoclonal antibodies are derived from cells that are identical because they are cloned from a single cell and then replicated. They are produced from animal tissue, most commonly laboratory mice. Humanized monoclonal antibodies are antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans. All monoclonal antibodies end with "mab," and a number have shown promise in MS.

## Rituxan® (rituximab)

**Company:** Genentech and Biogen Idec

Administered via intravenous infusion.

Rituxan is a monoclonal antibody (CD20, from mouse tissue) that binds to a receptor on the surface of B cells. These cells are then destroyed and their levels in the circulation are decreased. It is approved for use in the treatment of many lymphomas, leukemias, and autoimmune disorders.

A Phase I/II double-blind study of 80 people with low-inflammatory SPMS, sponsored by the National Institute of Neurologic Diseases and Stroke, is testing Rituxan versus placebo (RIVITaLISe). The study is still recruiting participants. The primary outcome measure will be the progression of brain atrophy after two years of treatment, unless predetermined analysis shows that the secondary outcome measures of MRI and clinical assessment are more reliable measures of effectiveness than brain atrophy.

A Phase II trial examined the effect of a single course of treatment in RRMS, 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 was also tested in 30 people with RRMS who had experienced continued clinical activity despite treatment with one of the approved disease-modifying therapies. Participants received two doses of Rituxan, two weeks apart, while continuing to take their usual medication. MRI scans were performed to look for areas of inflammatory lesions at weeks 4, 12, 16, 18, and 24. Multiple Sclerosis Functional Composite (MSFC) and EDSS scores were obtained at baseline and throughout the post-treatment follow-up to determine changes in function and mobility. Gadolinium-enhancing lesions were reduced after treatment with Rituxan; 74 percent of post-treatment MRI scans were free of gadolinium-enhancing activity as compared with 26 percent free of gadolinium-enhancing activity at baseline. Median gadolinium-enhancing lesions were reduced from 1.0 to 0, and there was an 88-percent reduction in the mean number of these lesions. The MSFC improved, while the EDSS remained stable.

Serious adverse events have been reported in Rituxan-treated patients with other diseases, including Progressive Multifocal Leukoencephalopathy (PML), an often-fatal viral infection of the brain (as with Tysabri); patients must be closely monitored.

## Lemtrada® (alemtuzumab, formerly Campath)

**Companies:** Sanofi, Genzyme, and Bayer HealthCare Pharmaceuticals

Administered in one course yearly by intravenous infusion over three-to-five consecutive days. The drug is a humanized monoclonal antibody that targets a protein present on the surface of mature lymphocytes and is approved for the treatment of B-cell leukemia.

This drug was granted Fast Track status by the FDA in June 2010.

The CAMMS223 Phase II study of 334 individuals with early, active RRMS compared Lemtrada to high-dose Rebif (44 mcg) in RRMS. In a three-year safety and efficacy trial, Lemtrada was more effective than Rebif at reducing the relapse rate and the risk for 60-month sustained accumulation of disability in patients with RRMS. In fact, the relapse rate in patients on Lemtrada is about one attack in nine years. This is the lowest relapse rate ever reported for an MS drug. More than 50 percent of the Lemtrada-treated patients actually improved. Lemtrada significantly reduced progression of brain atrophy in the second year of treatment, and trended toward reduction of brain atrophy over the entire two- and three-year periods.

In a fourth-year extension study of 334 individuals who participated in the original CAMMS223 study, Lemtrada yielded a 73-percent reduction in risk for sustained accumulation of disability, while 77 percent of Lemtrada-treated patients were relapse-free. A five-year assessment showed that 87 percent were free of sustained disability accumulation, 72 percent were relapse-free, and 65 percent were free of clinical disease activity.

These data indicate that Lemtrada's treatment effect is durable; it halts clinical disease activity in a significant proportion of RRMS patients through five years, with most patients last treated with Lemtrada at month 12 of the first year of study.

The CARE-MS I Phase III study of 581 individuals with RRMS was completed in April 2011. It met one of its two primary endpoints by reducing relapse rates by 55 percent in a two-year study that compared two annual cycles of Lemtrada against standard subcutaneous dosing of Rebif.

The Phase III CARE-MS II study of 840 patients with RRMS was completed in September 2011 and data should be released by the end of the year. It has a similar design to CARE-MS I, but focuses on patients who continue to have disease activity while taking currently approved disease-modifying therapy.

A Phase III extension study of approximately 1,500 individuals who participated in the CAMMS223 and the earlier Phase II CARE-MS I and CARE-MS II studies is ongoing. Scheduled from August 2009 to September 2014, it examines long-term safety and efficacy in patients who received Lemtrada, Rebif, or both in one of the prior studies. It will also determine if and when further Lemtrada treatment is needed, as well as the safety and efficacy of this as-needed treatment.

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.


**For years, Bayer® has been helping people** with relapsing forms of multiple sclerosis (MS) understand their treatment options and manage their treatment. Here are some things you should know about BETASERON (interferon beta-1b) and the BETAPLUS® Patient Support Program:

- Early treatment with BETASERON may help delay disease progression[1]
- With 20 years of clinical experience, BETASERON is the longest-studied MS therapy
- BETASERON offers every-other-day dosing with the thinnest needle available in MS therapy[2]
- Only BETASERON comes with BETAPLUS—a FREE support program including 24/7/365 access to an MS-trained BETA Nurse
- Only BETASERON offers $0 monthly copays* to help make treatment affordable

## 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

- **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.
- Severe hepatic injury, including cases of hepatic failure, has been reported. Patients should be monitored for liver enzyme elevations while taking **BETASERON**.
- **BETASERON** should be used with caution in patients with seizure disorders or cardiac disease.
- Female patients should be warned about the potential risk to pregnancy.

* 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.** BETASERON (prescribing information). Montville, NJ: Bayer HealthCare Pharmaceuticals Inc; 2010.

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

MEDICATION + SUPPORT™

## for the road ahead.

**Call 1-800-788-1467 any time or visit us online at BETASERON.com**

- Cases of anaphylaxis have been reported rarely.
- 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 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.

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

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.

**Please see brief summary of Medication Guide on the following page.**

Bayer HealthCare
Pharmaceuticals

Model used for illustrative purposes only.

 521-10-0007-10 Printed in USA. December 2010

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.

Manufactured by:
Bayer HealthCare Pharmaceuticals

Bayer HealthCare Pharmaceuticals Inc.
Montville, NJ 07045

U.S. License No. 1778



Part Number 6800503BS Revision Date 5/10

## Zenapax® (daclizumab)

**Company:** Biogen Idec, Inc and Abbott Laboratories

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

Zenapax is a genetically engineered monoclonal antibody that binds to CD25, a receptor on T cells that is thought to become activated in response to MS. Daclizumab is believed to work by selectively targeting these activated T cells without causing general T-cell depletion. 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 taking one of the approved interferon therapies. The study showed that Zenapax was well tolerated when added to an interferon. A 25-percent reduction was seen in the frequency of gadolinium-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 IIb SELECT trial, with 600 participants who have RRMS, is scheduled for completion in September 2015. It is a one-year study that will be assessing the safety and immunogenicity (the incidence of the development of antibodies) of extended treatment with daclizumab, administered by subcutaneous injection. The study includes three treatment arms, with two dose levels (at 150 mg and 300 mg) and a placebo group. Participants who complete this trial will be enrolled in an extended trial that will evaluate long-term safety and efficacy.

Preliminary results of the SELECT trial announced in August 2011 indicated that the annualized relapse rate was decreased by 54 percent in the 150-mg-dose group and by 50 percent in the 300-mg-dose group. It also met its secondary endpoints; the number of new gadolinium-enhancing lesions was reduced by 69 percent and 78 percent, the number of new or newly enlarging T2 hyperintense lesions was reduced by 70 percent and 79 percent, and the proportion of patients who relapsed was reduced by 50 percent and 51 percent, all for the low- and high-dose groups respectively. Sustained disability progression at one year was reduced by 57 percent with the lower dose and 43 percent with the higher. Additional analyses are ongoing.

A Phase III study with 1,500 participants will compare Daclizumab High Yield Process (DAC HYP) to Avonex. DAC HYP is administered subcutaneously once every four weeks for 96 to 144 weeks in a dose of 150 mg as compared to a weekly 30-mcg intramuscular injection of Avonex. The study is currently recruiting patients; it began in March 2010 and is scheduled for completion in January 2014. Outcome measures include relapse rate, functional decline and disability progression, and quality of life.

Daclizumab appears to be well-tolerated. Reported side effects include infections and abnormal liver function tests, diarrhea or constipation, and swelling of the extremities (bloating).

## Ocrelizumab

**Company:** Genentech, 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 a more humanized antibody than Rituxan.

In a Phase II study of ocrelizumab in 220 patients with RRMS, reductions in the total number of brain lesions detected by MRI scans (the primary endpoint of the study) were highly significant at 96 percent for 2,000-mg ocrelizumab and 89 percent for 600 mg compared to placebo. The annualized relapse rate was significantly lower versus placebo at week 24, with a reduction of 73 percent for ocrelizumab 2,000 mg and 80 percent for ocrelizumab 600 mg. Ocrelizumab's effectiveness was maintained through week 72; the proportion of relapse-free patients at week 72 was 84 percent for the 600-mg group and 82 percent for the 2,000-mg ocrelizumab group. Long-term safety data are not yet available.

The Phase III ORATORIO safety and efficacy study of ocrelizumab in 630 patients with PPMS is currently recruiting participants. Patients will receive either ocrelizumab (300 mg given intravenously in two infusions separated by 14 days in each treatment cycle) or placebo. The study is scheduled for March 2011 to August 2017. The primary outcome measure is time to onset of sustained disability progression (for at least 12 weeks); secondary outcome measures include the time to sustained disability progression (for at least 24 weeks), change in the total volume of T2 lesions (as seen on MRI), as well as safety, tolerability, and the incidence of adverse events.

A Phase III study to evaluate the safety and efficacy of ocrelizumab in comparison with Rebif in 1,000 individuals with RRMS is not yet open to participants. It was scheduled to begin in April 2011 and for completion in November 2014. The primary outcome measure is annualized relapse rate; secondary measures include time to onset of sustained disability progression, the proportion of relapse-free patients, MRI measures of disease activity, and change in MSFC Scale.

## 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 areas of investigation suggests that Vitamin D may be one underlying common factor that begins to make sense of the large amount of data on the geographic distribution of susceptibility to MS.

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

Following a review published in 2010, cumulative evidence led to a number of new clinical trials, mostly using Vitamin D as an add-on to existing therapies in Phase IV studies.

Published in August 2011, an important MS breakthrough has found that Vitamin D directly terminates production of disease-causing proteins. When Vitamin D is given to mice with EAE (an animal model of MS), it blocks the gene that encodes IL-17, stopping its production. IL-17 appears to be a major inflammatory component in MS. This breakthrough also demonstrates that Vitamin D increases suppressive T cells that combat inflammation.

A Phase II study that is currently recruiting participants is investigating whether Vigantol® oil, a form of Vitamin D hormone supplement (cholecalciferol), provides any added benefit when given in conjunction with Rebif. The study will have 348 participants; it began in February 2011 and is scheduled for completion in March 2014. Primary outcome measures are the mean change from baseline in the total volume of T2 lesions at week 48 and the proportion of relapse-free subjects at week 96. Secondary outcome measures include sustained disability progression, MRI measures of disease progression, the proportion of subjects free from disease activity at 96 weeks, and changes in cognitive function.

The French CHOLINE Phase II study of 250 individuals with RRMS who are receiving ongoing treatment with Rebif began in January 2010 and is scheduled for completion in December 2013. Its primary outcome measure is a reduction in relapse rate; secondary outcome measures include the time to a first documented relapse, the mean number of relapses per subject per year, the number of relapse-free patients after two years of treatment, MRI measures of progression and lesion load, and change in quality of life.

A Finnish Phase IV study with 70 participants is investigating cholecalciferol (Vitamin D3) as an add-on treatment to Betaseron in RRMS. It began in March 2008 and was scheduled to end in June 2011. Its primary outcome measure is biochemical; a secondary measure is the number of gadolinium-enhancing lesions and/or new enlarging lesions.

A small Phase IV study of 100 individuals with RRMS being treated with beta interferon has as its

## Vitamin D3 (continued)

primary outcome measure whether Vitamin D supplementation may reduce or eliminate flu-like symptoms and injection-site reactions from the interferon. It will also determine any effects on EDSS progression, relapse rate, and quality of life. The study began in October 2010 and is scheduled for completion in October 2011.

A small Phase I study in 40 individuals with MS, designed to determine the safety and immunologic effects of supplementation with low- (400 mg) and high-dose (10,000 mg) cholecalciferol (Vitamin D3), is currently recruiting participants whose serum levels of Vitamin D indicate that they are good candidates for supplementation. The study began in March 2010 and is scheduled for completion in December 2011. The primary outcome measure is to determine the safety of high-dose cholecalciferol and to assess the effects of cholecalciferol supplementation on serum immune markers; its clinical effects will also be assessed.

## Tovaxin™

**Company:** 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.

The TERMS placebo-controlled, one-year study in 150 patients with CIS and RRMS to evaluate Tovaxin's efficacy, safety, and tolerability has been completed. 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.

There was an annualized relapse rate of 0.34 per year (or one relapse roughly every three years) in the placebo group and 0.21 per year (or roughly one relapse every five years) in the Tovaxin group, representing a 37-percent decrease. There was also a 42-percent reduction in new gadolinium-enhancing lesions. The drug was well tolerated with mild skin reactions in some patients; no serious safety concerns were raised by this study.

In 70 patients who had at least one relapse in the 12 months prior to enrolling in the study and who had no previous exposure to MS therapy, Tovaxin reduced their annualized relapse rate by 64 percent compared to placebo. The overall annualized relapse rate for Tovaxin-treated patients dropped to 0.18 relapses per patient per year by the end of the 52-week study (this is slightly less than one relapse every five years). Additionally, 76 percent of Tovaxin-treated patients remained relapse-free at one year compared with 60 percent of placebo patients.

A larger study in RRMS patients is planned.

## Tetracycline Antibiotics

The tetracycline antibiotics, including minocycline and doxycycline, have immunomodulatory and neuroprotective activities. They appear to decrease the passage of lymphocytes across the blood-brain barrier. A small Phase II 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 with 200 participants is studying the effect of 100 mg of oral minocycline twice daily on the conversion of clinically isolated syndrome (CIS) to a diagnosis of MS at six and 24 months. It began in January 2009 and is scheduled for completion in December 2015. It will determine whether 100 mg of oral minocycline twice daily reduces the conversion of clinically isolated syndrome (CIS) to clinically active MS and if any treatment benefit seen after six months is maintained at two years.

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.

## BHT-3009

**Company:** 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 decrease the response of the 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 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.

# New Directions in MS Research

## Biomarkers

In medicine, the term *biomarker* refers to anything that can be used as an indicator of a particular disease state; in effect a biomarker is a *surrogate* for the disease state. It often refers to a protein measured in blood, whose concentration reflects the severity or presence of disease and/or that can be used to measure therapeutic effectiveness.

Although the term itself is relatively new, biomarkers have been used in medicine for many years. For example, body temperature is a well-known biomarker for fever, blood pressure helps determine the risk of stroke, and cholesterol levels are a biomarker and risk indicator for coronary and vascular disease. Biomarkers are often seen as the key to the future of what is termed *personalized medicine*. This refers to treatments that can be individually tailored to specific patients for highly efficient intervention in disease processes.

The search for biomarkers of MS is referred to throughout this article, and studies are ongoing for all major MS drugs to find markers that will help determine who should be treated with that drug as well as how effective the drug is after therapy is begun. The ultimate goal of these studies is to be able to decide which patient is most likely to respond to which drug, and then to follow him or her to see if the drug is working.

For example, current studies are showing that it may soon be possible to determine who might be a suboptimal responder to interferons, based on immune system-related substances that can be measured in the blood. A small study was designed to evaluate whether the type of cytokine present prior to treatment with Copaxone might act as a biomarker to identify those individuals with RRMS who are more likely to respond to immunomodulating treatments. It showed that people who responded to Copaxone secreted higher levels of specific inflammatory cytokines prior to treatment. The JC virus antibody test discussed earlier in the section on Tysabri is a good example of using a biomarker – the antibody – to indicate that the individual was previously exposed to this virus and may be more likely to develop PML.

There is a strong link between biomarkers and genetics, and the line between them may sometimes appear blurred. This is because many of the biomarkers that are being discovered relate to the activity of specific genes that code for proteins involved in inflammation, or are otherwise linked to the response to disease-modifying therapies. Studies of the *gene expression signature*, through *global gene expression analysis*, reveals the pattern of the entire DNA in an individual. This type of study has become possible due to recent advances in high-speed genetic pattern analysis. For example:

- Genes found to be differently expressed in MS effectively become biomarkers for disease progression and may change as the result of treatment. A recent study identified several candidate genes that could potentially serve as biomarkers of interferon treatment or targets for therapeutic intervention in MS.
- A study using gene expression analysis of whole blood showed significant differences in

# Who's Your LifeLine?

## A *LifeLine* is someone living with multiple sclerosis or an MS caregiver whose positive attitude, determination and achievements inspire YOU.

Recognize your LifeLine by submitting a nomination on **www.mslifelines.com/WYLL** Your story may be featured on the site!

*"Telling Will I had MS was difficult. I wasn't sure if it would scare him away, so finding the right words was tough. Thankfully, he made it easy. We got married, and he continues to inspire me to fight MS at every turn."*

Rashinda was diagnosed with relapsing remitting MS just before her 30th birthday. After a few difficult years, she met the man who became her husband and her LifeLine: Will.

The Who's Your LifeLine? recognition program honors individuals impacted by MS who focus on maintaining a positive outlook and do not allow MS to stand in the way of attaining their goals and dreams.

MS LifeLines

Services sponsored by EMD Serono

expression profiles of patients with optic neuritis compared with healthy controls.

- Another study showed that interferon therapy induces the expression of genes involved in interferon regulation and signaling; a subgroup of patients who tended to have a higher risk for relapses showed a different expression of specific genes.

An ongoing clinical trial sponsored by the National Institutes of Health is studying 1,200 individuals with RRMS who are participating in the MS-CombiRx study; this includes patients on interferon only, Copaxone only, or a combination of both. Samples of serum and white blood cells will be obtained from each patient prior to the study and at regular intervals thereafter. This study will identify biomarkers (genes and proteins) and link them to clinical- and MRI-linked parameters, such as the extent of inflammation and rate of disease progression. It will examine how the biomarkers may be related to disease development and progression as well as differences among patients' symptoms and response to treatment.

## Genetic Studies

As discussed in this article in previous years, there has been a growing body of evidence for the genetic component in MS. The studies on biomarkers have arisen as the result of this work, and a number of genes that are linked to the development of MS have been identified.

This field of research took a "giant leap forward" in August 2011, when the journal *Nature* published the results of the largest MS genetics study ever undertaken. A global collaboration of scientists identified 29 new genetic variants associated with MS, and confirmed 23 others that had been previously associated with the disease. The study confirmed that the immune system plays a major role in the development of MS: most of these genes are related to immune function, and more than one-third of them have previously been confirmed to be associated with other autoimmune diseases, such as Crohn's disease and type 1 diabetes.

The study involved nearly 10,000 people with MS and more than 17,000 controls without MS, in 15 countries. The research was carried out by approximately 250 investigators. The results are now to be confirmed and expanded in a second large-scale study.

The team found that a large number of these genes are related to T-cell function; they were mainly associated with T-cell activation and proliferation. This was particularly important because these are the cells believed to be the major mediators of the early immune attack on the brain and spinal cord in MS. Two of the genes are linked to Vitamin D, and low Vitamin D levels have already been implicated as a risk factor for developing MS. More than one third of the genes are known to be associated with autoimmune diseases such as Crohn's disease and type 1 diabetes; MS is believed to be an autoimmune disease as well.

The results of these and other genetics studies do not as yet significantly improve our ability to provide genetic counseling to individuals concerned about their risk of developing MS. However, they should help researchers to better define the biological pathways that lead to the development of MS. It is also hoped that they will enhance our ability to design better treatments for early MS.

## New Therapies under Investigation

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

### GENERAL THERAPIES

**Neuroprotective agents:** The term "neuroprotection" refers to strategies designed to prevent irreversible damage from a variety of cell types in the central nervous system (CNS), as well as to promote regeneration after MS-related damage has occurred. These have the goal of preventing the development of disability. A variety of neuroprotective strategies are now being studied.

One that seems especially promising is to identify the role that the neurotoxic transmitters glutamate and nitric oxide play in the development of neuronal damage, with the goal of preventing this process. At the same time, studies are focusing on stimulating growth factors that promote neural function, such as brain-derived neurotrophic factor (BDNF). This combination – decreasing factors that cause damage while at the same time increasing factors that stimulate growth – holds significant potential for preventing MS-related damage and stimulating neuronal function.

**Bone-marrow derived, stem-cell transplantation:** Based on encouraging results from a variety of studies, clinical trials are now starting to enroll patients. They involve both bone-marrow-derived stem cells, from which white blood cells developed, and mesenchymal stem cells, which are derived from tissues other than bone marrow.

### NEW CLINICAL STUDIES

These very brief snapshots of highly technical concepts will warrant more in-depth explanations in the future, if pilot clinical trials are encouraging. More information on these drugs may be found on the Internet.

**Cyclophosphamide (Cytoxan®):** The use of high-dose cyclophosphamide to treat progressive MS predates release of the first DMT in the early 1990s. Its toxicity has limited its use, and it is now used mostly as a "rescue therapy" for progressive disease that has not responded to more than one of the approved DMTs. Research on its use in progressive MS is still ongoing.

**Erythropoietin:** Erythropoietin is a hormone produced by the kidneys that promotes the formation of red blood cells in the bone marrow. It has shown neuroprotective effects in animal studies. A German Phase I/IIa pilot study suggests that high-dose treatment, but not a lower-dose regimen, leads to clinical improvement of motor function. Cognitive performance was also improved. Studies are ongoing.

**Idebenone (Catena®, Sovrima®):** This experimental drug was initially developed to treat Alzheimer's disease and other cognitive defects. It is being explored in MS because *oxidative stress* has been postulated to play a role in the death of myelin-producing cells, which has been linked to MS progression. A double-blind, placebo-controlled Phase I/II clinical trial of idebenone, sponsored by the National Institute of Neurological Disorders and Stroke, is currently recruiting participants with PPMS with little to moderate disability. It began in July 2009 and is scheduled for completion in May 2015.

MIS416: This "therapeutic vaccine" is a potent activator of the *innate immune system*, which provides immediate defense against infection but does not result in long-lasting or protective immunity. It has been primarily tested in cancer and acquired infections, with the goal of enhancing the inherent capability of a person's immune system to fight disease. An ongoing Phase I/II study will evaluate the safety and tolerability of IV-administered MIS416 in people with either PPMS or SPMS. Although this is primarily a safety study, effects on progression as measured by MRI and clinical status will be made at six months.

Masitinib: This drug targets mast cells, which are involved in allergic responses, wound healing, and defense against infection. It has been tested in a small group of patients and more data should be forthcoming in the next year.

MN-166 (ibudilast): This orally administered small molecule appears to have neuroprotective and anti-inflammatory properties.

Oral recombinant ovine interferon tau: This interferon decreased the number of new gadolinium-enhancing lesions during a nine-month period in individuals with RRMS.

Transdermal Administration of Peptides: A small Polish study of 30 individuals with RRMS evaluated the efficacy and safety of transdermal (skin patch) administration of two dose levels of three myelin peptides: MBP 85-99, PLP 139-151 and MOG, versus controls. In the lower-dose group, which received 1 mg each of the three peptides, the annual relapse rate at one year was reduced by 65 percent compared with placebo, progression in the EDSS was slightly lower, and 56 percent were relapse-free versus 10 percent in the placebo group. The treated group also showed a decrease in gadolinium-enhancing lesion volume and T2-lesion volume. The treatment was safe and well-tolerated. This approach will be pursued in future studies.

## OTHER AGENTS

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 the following experimental treatments:

- RTL1000 is a protein that inhibits the activation of myelin-reactive T cells, preventing the release of inflammatory cytokines and causing the release of anti-inflammatory cytokines.
- BAF312 and CS-0777 are S1P receptor modulators, in the same class of drugs as Gilenya. Both drugs are in ongoing preclinical studies. They cause a transient, dose-dependent decrease in circulating lymphocytes (immune-system cells produced to fight infection and disease) and T and B cells.
- CGP77116 is a small protein similar to myelin basic protein (MBP) and designed to modify the immune reaction that destroys myelin.
- SB-683699 is thought to reduce the number of active white blood cells entering the brain.
- RG2007 may block a T-cell pathway involved in MS.
- MK0812 targets proteins known as chemokines that attract immune-system cells to areas of inflammation.
- Symadex inhibits a pathway involved in macrophage maturation.

- Atacicept (ATX-MS-1467) is a "cocktail" of four peptides derived from human myelin basic protein that appears to block the development of mature B cells and inhibits the survival of antibody-producing cells.
- Anti-Lingo-1 (BIIB033) is a monoclonal antibody now being readied for its first human Phase I trial; animal studies showed that it promotes spinal cord remyelination and axonal integrity in the animal model of MS (EAE).

## Closing Notes

In summary, the future of disease-modifying therapies (DMTs) for MS continues to be promising, both in terms of new information about currently approved DMTs and exciting results for emerging therapies.

Advances in genetic and biomarker studies hold the promise that, in the future, it will be possible to identify which patients should be treated with specific therapies, and to better evaluate their response to therapy.

As always, your personal healthcare professionals will be your best guides to making the right decision for you.

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**. ◆

# 2012 MSAA Art Showcase

Melanie Bassett,
***Indian Yellow Summer***
2011 Art Showcase

*The theme of the **2012 MSAA Art Showcase** is "**Change**." 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 2012, in recognition of MS Awareness Month.*

***Submissions will be accepted between October 1 and December 15, 2011.***

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

*For more information, contact:*

*Jaime Smith*
*MSAA*
*706 Haddonfield Road*
*Cherry Hill, NJ 08002*
*Email: jsmith@msassociation.org*
*Phone: (800) 532-7667, ext. 146*

# Ask the Doctor

By Dr. Jack Burks
Chief Medical Officer for MSAA

## Resolving Injection-Site Reactions

*Dr. Jack Burks*

**Q:** I've been on Copaxone® since October 2010. I have large (1/2 palm-size) purple patches and (dime-size) bruising at every area where I inject, and these have not gone away. I use the auto-injector and have tried various depths. I live near extensions of Denver's Rocky Mountain MS Center and Colorado Neuro Institute facilities.

**A:** This is a serious problem and needs expert attention to allow you to keep taking Copaxone. You are fortunate to live near the Rocky Mountain MS Center. I would request to have a doctor or nurse specialist from the center evaluate these skin reactions. Take your injector with you so the nurse can observe your technique and make sure that the auto-injector is working properly. Another option would be to speak to the pharmaceutical patient program's nurse supervisor and explain your situation.

With regard to your injections, you should avoid injecting directly into the skin. You need to make certain that the needle penetrates through the skin and into the subcutaneous (fatty) tissue layer. Be sure that the needle is dry to make certain that no medication is on the outside of the needle, which may cause skin irritation.

**Q:** I am a 66-year-old woman diagnosed with MS in 1983. I have had unrelieved chronic neuropathic pain for five years, and have had epidurals, cortisone injections, neuro-stimulators, Marinol®, and have seen an orthopedic doctor. Do you have any suggestions? Would Botox® help?

**A:** Many MS patients suffer from neuropathic pain/dysesthesias/parenthesis. However, you have not mentioned the treatments that I recommend. The first is ice packs or cooling vests, etc. The next approach is medication for seizures and other pains such as gabapentin (Neurontin®), pregabalin (Lyrica®), duloxetine (Cymbalta®), carbamazepine (Tegretol®), and others.

Capsaicin ointment is another medicine that helps some people. Acupuncture and massage are adjunct treatments that may also be effective. If your pain is related to muscle spasms, then a Botox injection might be helpful. Other treatments for muscle spasms, such as oral or intrathecal baclofen, tizanidine (Zanaflex®), or similar medications, may help as well. Talk to your MS doctor for his or her specific treatment recommendation.

**Q:** I was 33 when diagnosed with MS almost two years ago. I had been experiencing numbness and tingling, and was prescribed 1,000 mg daily IV infusion of Solu-Medrol® for five days. My only previous experience with

**steroids was with 10 mg oral prednisone, and I experienced shortness of breath and chest tightening. I was given Tylenol® and a Benadryl® for any allergic reaction and then began the IV infusions. One day after stopping the Solu-Medrol, I had an IPH brain hemorrhage stroke on my left side. Have you ever experienced any problems similar to this? Also, this incident delayed my starting Rebif® until July of 2010, following an MS attack in May. My MRI at that time showed new lesions. Could the delay in treatment have caused these new lesions or attack?**

**A:** I have not encountered a brain hemorrhage after steroids in my 40 years of seeing MS patients and treating hundreds of MS patients with steroids. I could not find any references in the medical literature that documented such an event. I feel very badly for you. In my opinion, steroids seem like the appropriate treatment for your symptoms.

I can understand the reluctance for not starting Rebif (or any other MS treatment) for a time period after your stroke, even though you had active MS and were susceptible to a flare-up of your MS. People with MS on Rebif or other DMT have a reduced risk for MS attacks. However, none of these drugs cure MS, prevent all attacks, or stop MRI lesions. Your stroke complicates the issue. I hope your MS has settled down on Rebif and you have recovered from your stroke.

**Q: How is one's sex life affected by MS? In our case, the relationship is good, but I am suffering because of our lack of intimacy. My husband has decided to sleep in a separate bedroom. Although he remains faithful, he doesn't want to go for outside help. Can you give me any advice?**

**A:** Lack of sexual intimacy plagues many couples, with or without MS. MS can cause significant sexual problems in both men and women. The most frequent issues for couples are the lack of understanding and communication between spouses. Men with MS are often helped by drugs (like Viagra®, Cialis®, and Levitra®), an injection into the penis, a vacuum pump, an implant, etc. Women are often helped by a good personal lubricant, vibrator, etc.

Decreased libido, muscle spasms, and painful intercourse can occur with either gender. Anxiety, low self-esteem, depression, change in body image, fear of rejection, fear of inflicting pain, medications, embarrassment, urine leakage, lack of sensation, fatigue, poor understanding of alternative sexual positions, and different ways to get sexual gratification affect sexual intimacy. Other physical and psychological issues may also interfere.

I would try to discuss the subject in an open, non-accusatory way with your spouse. Then I would bring up the issue with your MS doctor who can evaluate the physical issues, if any, and can refer you to a psychologist or sex educator, as needed. ◆

*Jack Burks, MD is the chief medical officer for MSAA. He is an international MS neurologist, writer, lecturer, and researcher, who assists with the development of new MS therapies.*

by Susan Wells Courtney
Reviewed by Jack Burks, MD

# CCSVI Update

## Background Information on CCSVI and MS

Many questions still surround the possible connection between chronic cerebrospinal venous insufficiency (CCSVI) and multiple sclerosis (MS). CCSVI is a complex condition involving changes in blood flow from the brain back to the heart, which some researchers theorize could possibly lead to 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 (extracranial cerebrospinal veins) – those designed to transport blood from the brain back to the heart – collapse and/or become blocked, a condition known as "stenosis." Studies have shown that when the normal blood flow is altered, especially when the flow of blood is reversed, the body may react with an inflammatory response.

Two years ago, Paolo Zamboni and others published the results of a pilot study in the December 2009 edition of the *Journal of Vascular Surgery*. In this article, lead investigator Dr. Zamboni describes an experimental procedure to widen the narrowed or blocked veins in a study of 65 MS patients. Some refer to this as the "liberation procedure," where angioplasty is performed using a tiny balloon inserted into an affected vein. From this small, open-label study, Dr. Zamboni noted that a portion of the patients with relapsing-remitting MS (RRMS) experienced fewer relapses and improvement in function.

Since these results were published, the CCSVI theory in MS has received a great deal of attention. While a small number of studies are underway, some MS patients are seeing vascular surgeons or interventional radiologists on their own to undergo speculative diagnostic and corrective procedures. Additionally, vascular specialists and neurologists are not always in complete agreement about the presence of this condition in patients with MS and the procedures.

Anecdotally, some individuals with MS who have undergone a procedure feel that they are experiencing some improvement in certain symptoms. Typically, these might include improvements in fatigue, heat sensitivity, sleep, concentration, and balance. Over time, some even attribute improvements in bladder issues, mobility, flexibility, and other symptoms to the procedure. Conversely, some patients did not see any improvement following the procedure.

## Research Challenges with CCSVI and MS

The problem faced by the medical community in researching the CCSVI theory is two-fold. First, researchers need to prove whether or not CCSVI occurs more often in individuals with MS versus the general population, and if so, how it may be related to the disease. Further complicating the issue

is the fact that no single procedure or protocol has been identified for its diagnosis, and a wide range of results can occur when using different imaging equipment, techniques, and technicians.

The second problem in researching the CCSVI theory involves treating the condition. Dr. Zamboni and others have used an angioplasty-type of treatment for opening closed veins with a tiny balloon that is inflated several times and then removed. Possible adverse events can include bleeding, heart arrhythmias, and rarely an allergic reaction to the dye used to illuminate the veins. Additionally, veins sometimes close (restenosis) in the months following the procedure. A second option is to insert a stent into the closed veins, which poses additional risks – such as the stent dislodging and moving to another area of the body – requiring immediate surgery. Even with the stents, scar tissue can sometimes form and clog the stent. Finally, doctors will still need to determine if and to what extent MS patients may benefit from such a procedure, and if the benefits outweigh the risks.

More than 50 articles on the subject have appeared in peer-reviewed publications over the past two years, although many present conflicting results – with some finding significant proof of CCSVI in MS patients, and others finding no evidence – a problem often blamed on the lack of a protocol for specific diagnosis. Doctors are also looking at possible relationships between CCSVI and known risk factors for MS, including Epstein-Barr virus, genetic factors, Vitamin D deficiency, and cigarette smoking.

Experts agree that a strict protocol for testing will need to be developed, that a combination of tests may be required for a confirmed diagnosis of CCSVI, and that the operators performing these tests will need specialized training for consistent results. Another impressive hurdle in these studies is the issue of blinding. The researchers, doctors, and operators performing the diagnostic tests and evaluating the patients after the procedures need to be blinded as to who has MS and who received the active treatment, or the results could be biased.

### Current Studies and CCSVI Registry

Studies may be found by visiting **www.clinicaltrials.gov** and searching for "CCSVI and multiple sclerosis." Many of the studies are listed as still recruiting participants, but interested individuals should check with the contact person listed for the most current information on recruitment. Currently, seven studies are listed, with locations in New York, Texas, California, Poland, and Italy. In June 2011, the Canadian Institutes of Health Research announced that they will be proceeding with a Phase I/II clinical trial.

One of the studies listed is sponsored by the Hubbard Foundation, titled, "Multi-center Registry for CCSVI Testing and Treatment." Located in San Diego, California, the purpose is to develop a registry of patients evaluated and treated for CCSVI, looking at changes in quality of life. The Hubbard Foundation is looking for doctors

and medical facilities that perform CCSVI testing and treatment to register under their IRB (Institutional Review Board) approval to conduct research and provide the outcome of those tested and treated for CCSVI.

In June 2010, the National MS Society and the MS Society of Canada committed more than $2.4 million to support seven new research projects focusing on the role of CCSVI in MS.

### Closing Remarks

As with any unproven theory and treatment, interested patients are strongly encouraged to talk with their doctor, and if appropriate, participate in an approved clinical trial. Without a tested and proven protocol for the diagnosis and treatment of CCSVI, individuals could be putting themselves at risk. In July 2011, news arrived of a second individual with MS from Canada who sought treatment outside of the country and died due to complications. Although such tragic results are not common, individuals considering these types of procedures should be aware of the risks involved.

MSAA enthusiastically but cautiously supports the investigation of potential causes and treatments for MS, striving to communicate such research to the MS community as soon as any information becomes available. However, MSAA's policy is to consider patient safety as the top priority – recognizing that all prospective theories and experimental treatments need to be thoroughly studied through rigorous clinical trials.

To view MSAA's other CCSVI articles, please visit **www.msassociation.org** and select "Recent News." Individuals may also speak with one of MSAA's Helpline consultants at **(800) 532-7667**.

For information on the specifics of CCSVI, and to learn about patient experiences, readers may visit the CCSVI Alliance's website at **www.ccsvi.org**. ◆

## *Botox® Approved for Urinary Incontinence*

On August 24, 2011, Allergan, Inc. announced that the United States Food and Drug Administration (FDA) approved Botox® (onabotulinumtoxinA) injection for the treatment of urinary incontinence. Specifically, the approval is for adults who experience detrusor over-activity resulting from a neurological condition such as MS, and who either do not respond adequately to or are intolerant of anticholinergic medications.

For individuals who experience episodes of urine leakage, this treatment may lead to a significantly improved quality of life. MSAA recommends that MS patients with an overactive bladder discuss this new treatment with their doctor.

For more information on the clinical trials and approval of Botox, please visit the "Recent News" section of MSAA's website at **www.msassociation.org** or visit **www.botox.com** for general drug information. Individuals may also speak with one of MSAA's Helpline consultants at **(800) 532-7667**.

# Female MS Volunteers Needed

## FOR A RESEARCH STUDY

The National MS Society and the National Institutes of Health (NINDS) are funding a team of investigators at fifteen medical centers across the U.S. to conduct a two-year, placebo-controlled clinical trial testing treatment with the estrogen of pregnancy (estriol) in MS. All 150 women with relapsing-remitting MS will take Copaxone® (glatiramer acetate, Teva Pharmaceutical Industries Ltd.) in combination with either oral estriol or oral placebo. Patients previously treated with an interferon or Copaxone® may be included.

The estriol trial is taking place at fifteen medical centers across the U.S. Women between 18-50 who are diagnosed with relapsing remitting MS and are interested in participating in this clinical trial should contact the nearest site to discuss their eligibility:

| **Institution** | **Coordinator** | **Phone** |
|---|---|---|
| UCLA; Dr. Barbara Giesser | Mike Montag | 310-794-4020 |
| Washington University, St. Louis; Dr. Anne Cross | Debbie Kemp | 314-362-3839 |
| UMDNJ, New Brunswick; Dr. Suhayl Dhib-Jalbut | Yaritza Rosario | 732-235-7099 |
| OSU, Columbus; Dr. Michael Racke | Andrea Schertzer | 614-366-3757 |
| University of Chicago; Dr. Anthony Reder | Mildred Valentine | 773-702-9812 |
| University of Utah, Salt Lake; Dr. John Rose | Julia Klein | 801-582-1565 x2014 |
| U. of Texas Southwestern, Dallas; Dr. A. Courtney | Gina Remington | 214-645-0560 |
| Johns Hopkins U., Baltimore; Dr. John Ratchford | E'tona Ford | 410-502-2489 |
| University of Colorado, Aurora; Dr. John Corboy | Haley Steinert | 303-724-4172 |
| U. of New Mexico, Albuquerque; Dr. Corey Ford | Lori Bachert | 505-272-8905 |
| U. of Pennsylvania, Philadelphia; Dr. Dina Jacobs | Vanessa Zimmerman | 215-349-5162 |
| Dartmouth Med. Sch., Lebanon, NH; Dr. E. Lallana | Laurie Rizzo | 603-653-9947 |
| U. of Kansas, Kansas City; Dr. Sharon Lynch | Kelly Dickerson | 913-588-0080 |
| U. of Minnesota, Minneapolis; Dr. Gareth Parry | Susan Rolandelli | 612-624-7745 |
| Mayo Clinic Arizona, Scottsdale; Dr. D. Wingerchuk | Irene Galasky | 480-301-6104 |

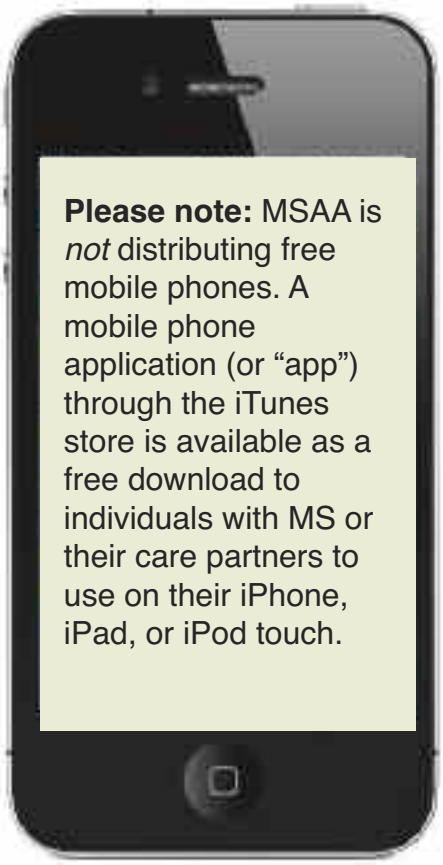
Contact: For more information, contact the study sites listed above, or please see the study's listing (NCT00451204) on ClinicalTrials.gov.

# Program Notes

By Peter Damiri
Senior Director of Programs

## Multiple Sclerosis – We've Got an App for That!

Launched this spring, MSAA's free application for mobile phones, ***My MS Manager***™, continues to generate tremendous interest and hundreds of downloads each month by the MS community. Currently available for iPhone, iPad, and iPod touch, this first-of-its-kind app for MS offers individuals a convenient and effective tool to manage the ever-changing course of the disease.



**Please note:** MSAA is *not* distributing free mobile phones. A mobile phone application (or "app") through the iTunes store is available as a free download to individuals with MS or their care partners to use on their iPhone, iPad, or iPod touch.

As a member of the MS community, *My MS Manager* allows you to input and store:

- Comprehensive medical records
- Your healthcare team's contact information
- Descriptions of MS flare-ups, tracking their duration, frequency, and intensity
- Information on side effects and effective treatment strategies
- Important details essential to staying one step ahead of your MS

Once you begin using *My MS Manager*, reports can be generated utilizing the activities and occurrences logged on your phone. These reports can also be shared with doctors and other members of your healthcare team via email updates and secure online access. Other features of the app include an up-to-date feed of MS-related news and links to MS resources, including MSAA events and contact information, plus a Google Map-powered locator to find nearby emergency care, physicians, or hospitals instantly from your mobile device.

As you may have read or experienced, MS healthcare providers continue to encourage patients to take an active role in managing the challenges and unpredictability of the disease. This concept of patient self-management is gaining widespread acceptance and MSAA has developed the *My MS Manager* app, along with our recent S.E.A.R.C.H.™ initiative (for learning about treatment options), to help provide you with the tools you need to better track, report, and manage the day-to-day challenges of MS.

As mentioned earlier, *My MS Manager* is available for iPhone, iPad, and iPod touch and may be downloaded at no charge through the Apple App Store. This may be accessed by visiting: **www.msassociation.org/mobile**.

MSAA hopes to expand the mobile app to additional platforms, including Android and Blackberry, in the future. ◆

By Neal Zoren
MSAA Director of Development

# The Power of Sustaining Gifts

Twelve times $20 equals $240. The math is basic. "Elementary," as Sherlock Holmes' friend Watson might say.

This simple equation turns into something very important when applied to charitable giving. It's the example that demonstrated to Amy, who has MS, how she could afford to make the significant annual gift she desired MSAA to have.

Amy wanted to donate $250, but the sum was too large for her budget. So MSAA told Amy about monthly giving, gifts we refer to as "sustainers," and showed her a way she could donate all she wished.

The method involved breaking Amy's total gift into affordable amounts that MSAA would receive monthly, quarterly, semi-annually, or any way she preferred. To make an annual gift of $250, Amy could arrange for monthly donations of $20. That would add up to $240, and if the extra $10 mattered to her, she could tag it on at any time during the year.

Once Amy set up this mode of giving, donations in the increments she chose would automatically be renewed every year. Amy contributed as she intended and stayed comfortably within her budget.

All of a sudden Amy was a "sustainer," a monthly donor whose annual gift qualified her as a major donor and placed her at the Steward level in MSAA's President's Circle, a group comprising the charity's most dedicated donors. The beauty of the sustainer is people can be as generous as they want and watch monthly gifts accumulate into a significant annual gift.

Here's how the "sustainer" works. The donor chooses the amount of his or her annual gift. That amount is divided into 12 equal parts that are either charged to a credit card or sent as an automatic payment from the donor's bank account as an electronic fund transfer (EFT).

**The part of sustaining gifts that donors and MSAA enjoy most is seeing the gifts accumulate and realizing the good that their gifts accomplish.**

The easiest way to establish a monthly gift is via MSAA's website, **www.msassociation.org**. Click the "Donate" button. This takes you to a page that features three options: general, memorial ("In Memory Of"), or tribute ("In Honor Of") gifts. Click on any of these, and a page appears on which you can enter the amount of your gift. Some amounts will be suggested, but you can choose the option that lets you enter any amount you wish. The final step is to check the box that asks if you want your gift to be applied monthly. That box is conveniently located below the optional amounts. Supply your credit card information, and you're all done.

Many people choose to be "sustainers" because they like the way a $5 monthly gift turns into a $60 annual gift. People also like the automatic renewal. Some of MSAA's "sustainers" have been making gifts monthly

since 2003, the year we established the program. Donors can drop out of the program any time they like just by calling or emailing us. Happily, most of the calls we receive are from people who want to refresh credit card information regarding expiration dates.

The EFT option can be arranged easily by talking to me or my colleague, Jaime Smith. It involves sending a voided check from the account from which you choose to draw. That is sent to our bank, and the amount you have written on the check will be automatically deducted from your designated account on the same date each month.

Although I refer to monthly gifts, an annual gift can be divided by any increment you choose. For example, you may divide the annual amount by four for a quarterly gift or by six for a bi-monthly gift. The part of sustaining gifts that donors and MSAA enjoy most is seeing the gifts accumulate and realizing the good that their monthly (or other time period) gifts accomplish.

Amy got her wish. She said she wanted to help others with MS and was grateful to find a way she could afford to do all that she intended.

If monthly giving appeals to you for the larger gift that will accrue or for the convenience of making an automatic sustaining contribution, please visit MSAA's website at **www.msassociation.org** or call me, Neal Zoren, at **(800) 532-7667, extension 128** or Jaime Smith at **extension 146**. We will be pleased to help you. ◆

# 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
Biogen Idec
Novartis Pharmaceuticals Corporation

## VISIONARIES *($50,000 to $99,999)*

Allergan, Inc.
Avanir Pharmaceuticals
Bayer USA Foundation
Genentech Foundation
Genentech, Inc.
Questcor Pharmaceuticals, Inc.

## INNOVATORS *($25,000 to $49,999)*

Medtronic Foundation

## ADVOCATES *($10,000 to $24,999)*

Catholic Human Services Foundation
The Chatlos Foundation
Genzyme Corporation
The Virginia Dashiell Foundation

# Finding Happiness Through Artistic Expression

**By Alba S. Morton, sister of David Olivencia**

David Olivencia, son of Wilson and Alba Olivencia, had an unveiling celebration for his first collage, entitled "Reflections," this past summer at the John L. Montgomery Care Center in Freehold, New Jersey. This event was attended by the residents, administration staff, family, and friends.

*David Olivencia at the unveiling of his collage, "Reflections."*

The John L. Montgomery Care Center serves the needs of residents from the ages of 18 and up, who suffer from a variety of chronic and debilitating conditions. It has a specialized Young Adult Program, where more aggressive therapies are provided for these residents.

In the early 1990s, a computer lab was added as part of the rehabilitation program. The lab is a wonderful addition, significantly enhancing the quality of life for the residents. The lab is equipped with handicapped-adapted computers so that residents with significant limitations are able to enjoy the many benefits of computer and internet access. With the support and the dedication of the lab manager and recreation team members, some of the residents, including David, spend many hours at the lab.

When David was physically well, one of his hobbies was photography. Even though David cannot use his hands because of the effects of multiple sclerosis, photography continues to be his passion. Through the eyes of an artist, David transforms his pictures stored in his computer into new images. By using Adobe® Photoshop® along with the help of a computer chip on his eye glasses, he modifies his pictures by altering the shapes and colors. Some of the altered pictures were used to create David's collage (shown above).

According to his mother, Alba, David's motto is, "When life gives you lemons, make lemonade." With the computer program at his residence and updated software, David told his mother that he didn't realize how much he was missing until he started using the new software, and looks forward to working on his computer throughout the day.

David's pictures have won numerous awards and his work continues to receive accolades and recognition. His collage is on display in the lobby of the John L. Montgomery Care Center. ◆

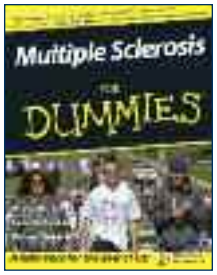
# Spread the Word

## *The Illustrated Guide to Assistive Technology and Devices*


*Written by Suzanne Robitaille*
*Published by Demos Health*
**MSAA Book #9**

Written by an accomplished journalist, this illustrated book highlights a wide range of devices designed to enable individuals with disabilities to live and function independently. Chapters are devoted first to the history of assistive technology, and then on to technologies to help individuals with visual, hearing, physical, cognitive/learning, and communications disabilities. Information is also included on the Americans with Disabilities Act (ADA), how to pay for assistive technology, the future of assistive technology, and a long list of resources.

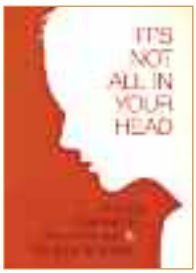
## *Multiple Sclerosis for Dummies*




*Written by Rosalind Kalb, PhD, Nancy Holland, EdD, RN, and Barbara Giesser, MD*
*Published by Wiley Publishing, Inc.*
**MSAA Book # 127**

This comprehensive reference is part of the "For Dummies" book series, which gears information for beginners. Written by experts in the MS field, this book presents a wealth of MS facts and advice in an easy-to-read format, often using bullets, checkmarks, and icons. It covers a host of topics, from diagnosis and symptom management, to staying healthy and planning for a future with MS.

## *It's Not All in Your Head: Anxiety, Depression, Mood Swings, and Multiple Sclerosis*




*Written by Patricia Farrell, PhD*
*Published by Demos Health*
**MSAA Book #7**

This book covers some of the basics about multiple sclerosis and ties them in with the emotional issues involved with the disease. The mind-body connection is discussed, along with "Riding the Rollercoaster" of MS. The author is a practicing clinician, medical writer, and disability consultant, who has been featured on national TV shows. Her writing is comfortable to read and incorporates many patient stories as well as research findings. The book also provides self-help techniques and coping strategies to give readers the tools they need to assist in regaining self-esteem, hope, and happiness.

## *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)**

# Has MS Impacted Your Wallet?

MSAA has partnered with the **National Disability Institute** to develop an **educational webinar series.** These programs are designed to help increase knowledge and utilization of financial management tools and available assistance programs.

**If your wallet could use some help, visit MSassociation.org to register for:**

| | |
|---|---|
| October 27: | Working Towards Financial Wellness |
| November 17: | Get Out There and Flex Your Financial Muscles |
| January 19: | Invest in Yourself |

***Support for these programs is provided by Acorda Therapeutics, Inc.***

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

CHANGE SERVICE REQUESTED

SIGN UP FOR

# EMAIL UPDATES FROM MSAA


## WHY SIGN UP?

By signing up to receive email from MSAA, you'll receive the latest alerts and information about MS-related news, events, and programs happening in your area and across the country, including:

- **New MSAA programs and services**
- **Invitations to educational programs and special events**
- **Research updates and information affecting the MS community**
- **Announcements about the latest MSAA publications**
- **Volunteer opportunities for MSAA within your community**
- **All the ways you can show your support to MSAA**

Go to **msassociation.org/emailupdate** to sign up today!