Decision Resources

Cognos Study #9

A Pharmacor Service

MULTIPLE SCLEROSIS 2005-2020

April 2007

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.5401.2615 ♦ Fax +81.3.5401.2617

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Executive Summary

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Executive Summary

Key Findings

- We forecast modest sustained annual growth—2.7%—of the MS market from 2005 to 2015. Annual market growth will slow to 0.9% from 2015 to 2020. Emerging oral agents will contribute substantially to market growth, accounting for 25% of major-market sales in 2020. Overall, all emerging agents will garner 32% of major-market sales in that year.
- A drug's safety profile has become instrumental to its market success. The history of fatal opportunistic infections associated with natalizumab (Biogen Idec/Elan's Tysabri) has not only impaired its once-promising market success but also made physicians much more cautious about emerging therapies.
- FTY-720 (Novartis/Mitsubishi Pharma's fingolimod) holds the greatest market potential of all emerging therapies for MS. Because of its moderate safety profile, improved efficacy over current therapies, and oral formulation, we expect FTY-720 to capture significant patient and market share by 2020 and achieve peak-year sales of $750 million to $1 billion.
- Although emerging agents will offer more therapeutic options to MS patients, significant opportunity remains in this market. The MS community continues to call for drugs that halt disease progression, promote remyelination and neuroprotection, and demonstrate improved safety, efficacy, tolerability, dosing regimens, and formulations.

What are the key parameters of the multiple sclerosis market?

Multiple Sclerosis: Key Findings

Current G7 Market Landscape		2005 Market Size		2020 Market Size	
Diagnosed patients:	524,700	US:	$2,721.4 MM	US:	$3,491.3 MM
Treated patients:	316,000	EU:	$1,277.2 MM	EU:	$1,992.0 MM
Phase II drugs:	21	JA:	$36.4 MM	JA:	$48.0 MM
Phase III/PR drugs:	5	Total:	$4,035.0 MM	Total:	$5,531.3 MM

Current Market Leaders	Patent/Exclusivity Expiry	2005 G7 Sales
Interferon-β-1a (Biogen Idec's Avonex)	2013 (US); 2005 (EU); 2005 (JA)	$1,359.2 MM
Glatiramer acetate (Teva Pharmaceutical's Copaxone)	2014 (US); 2015 (EU); 2015 (JA)	$1,006.9 MM

Most Important Unmet Needs	Current Attainment	Opportunity
Reversing neuronal damage	Low	High
Preventing disease progression	Low	High
Improved therapy for chronic-progressive MS	Low	High
More-convenient drug delivery	Low	High

Most Promising Emerging Therapies	Launch Date	Peak-Year Sales Potential
FTY-720 (Novartis/Mitsubishi Pharma's fingolimod)	2010	$750-1,000 MM
MBP-8298 (BioMS Medical)	2011	$250-500 MM

Key Events/Factors During Study Period	Impact on Market	Probability
Relaunch of natalizumab (Biogen Idec/Elan's Tysabri) in the United States and launch in Europe (2006)	+++	Not applicable
Launch of FTY-720 (2010)	+++	High
Launch of first oral agent (cladribine, 2010)	++	High
Launch of follow-on products to interferon-β agents and glatiramer acetate (2007-2009)	+	High
Launch of MBP-8298 for chronic-progressive MS (2011)	+	Moderate
Launch of biogeneric versions of the interferon-β agents (2012-2014)	-	High

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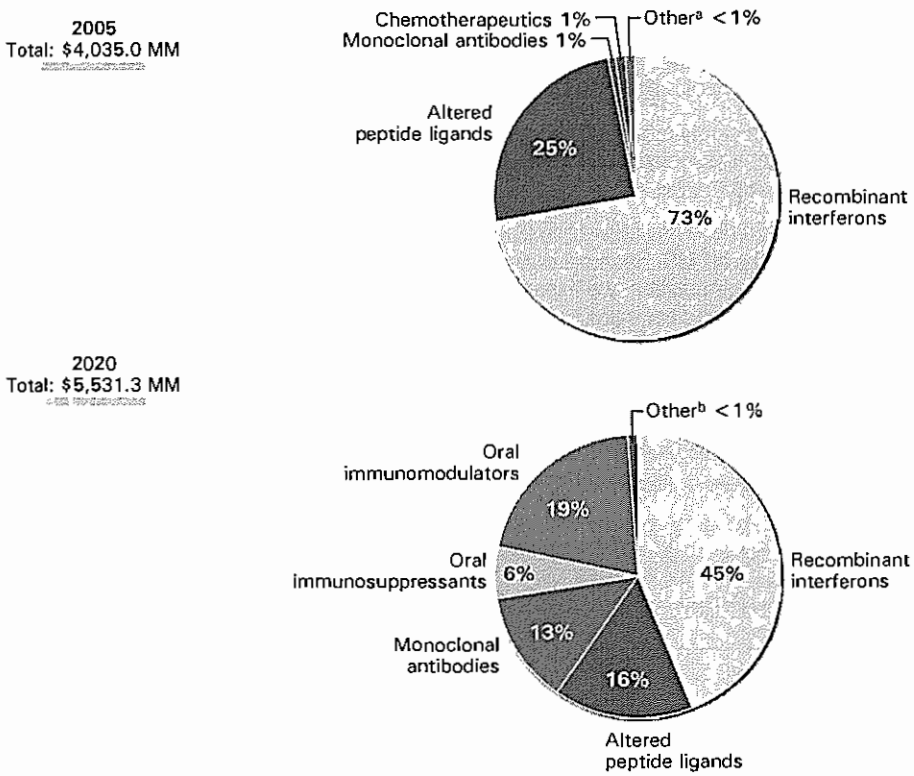
Source: Decision Resources, Inc.

Multiple Sclerosis Therapies, 2005-2020: Market Share



a. "Other" includes corticosteroids, azathioprine, and mycophenolate mofetil.
b. "Other" includes corticosteroids and chemotherapeutics.

Note: Percentages may not add to 100 because of rounding.

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What factors are driving the market for multiple sclerosis therapies?

- The MS market is growing as a result of increased diagnosis rates, which are fueled by increased use of the McDonald criteria and magnetic resonance imaging (MRI) as well as diagnosis occurring earlier in the disease process.
- Increasing drug-treatment rates will drive growth of the MS market through 2020 as expert opinion shifts in favor of prescribing therapy early in the disease. Indeed, patients with early forms of MS represent a significant commercial opportunity, and the interferon beta (IFN-β) agents are now approved for use in this population. In addition, therapies that launch during our study period will provide new therapeutic options, particularly to patients underserved by current therapies, including early-

stage MS patients, chronic-progressive MS (CP-MS) patients, and patients whose MS is refractory to or who cannot tolerate current therapies. The convenience provided by emerging oral agents will also promote use in patients who cannot tolerate or who do not want injectable therapies.

- The lack of cost-sensitivity in the MS market has historically driven emerging agents to be priced at a premium to current therapies. We expect this trend to continue during our study period; emerging therapies will command higher prices thanks to improvements in convenience or efficacy. As emerging agents compete with current therapies for patient share, their higher price points will drive sales growth.
- Two therapies in particular will contribute significantly to market growth through 2020: natalizumab (Biogen Idec/Elan's Tysabri) and FTY-720 (Novartis/Mitsubishi Pharma's fingolimod). With natalizumab's relaunch in the United States and launch in Europe in 2006 and FTY-720's expected launch in 2010 in the United States and 2011 in Europe, these drugs will garner substantial patient share because of their demonstrated efficacy and, in the case of FTY-720, availability in an oral formulation. However, these drugs' potential to trigger severe side effects will hamper uptake so that neither agent will achieve blockbuster status during our study period.
- Despite the parenteral formulation of current therapies, patient compliance is extremely high in MS, and the launch of agents in more-convenient oral formulations will only increase compliance. As the drug-treated population increases because of the availability of additional novel therapies, the percentage of patients who are compliant with treatment will increase, driving market growth.

What factors are constraining the market for multiple sclerosis therapies?

- Despite experts' demand for agents that are more efficacious at delaying disease progression, the majority of MS agents that we expect to launch during our study period have yet to demonstrate significant improvement in efficacy over most current therapies. As a result, most emerging therapies will capture limited patient shares and garner only modest market sales.
- Drug safety has become a primary consideration in medical practice following the unexpected development of fatal opportunistic infections in patients taking natalizumab, a development that prompted its temporary withdrawal from the U.S. market. Experts continue to be leery of natalizumab, and this guardedness over safety has extended to emerging therapies, even though these therapies have demonstrated adequate safety profiles thus far in development. This heightened awareness of the possibility of severe side effects will constrain uptake of new agents, relegating many of them to third- or fourth-line therapies.
- Reimbursement of MS therapies continues to constrain the market, particularly in Europe. Indeed, although natalizumab has been approved in all European markets we cover, reimbursement has been approved only

in Germany. This problem is due to the high cost per year of the drug, and until reimbursement issues are resolved, the drug will not be administered unless patients are willing to pay out-of-pocket, as has occurred in the United States. Given the obstacles that natalizumab is facing, emerging "me-too" agents with similar safety and cost issues may also have difficulty receiving reimbursement approval.

- The launch of biogeneric versions of the IFN-β agents will contribute to losses in market and patient shares of the respective branded forms. However, biogenerics face developmental and regulatory hurdles that will delay their entry into the market, especially in the United States, where regulatory frameworks have yet to be established. Once available on the market, their uptake will be modest; physician concerns over bioequivalence will likely be offset by the push from reimbursement agencies for biogeneric use.

What are the drug development activities of note in multiple sclerosis?

- Several drugs in the MS pipeline will fulfill a significant unmet need by offering the convenience of an oral formulation. The first oral agent to market will be Merck Serono's oral cladribine, launching in the United States and Europe in 2010, but four other oral agents will also launch during our study period: FTY-720, Sanofi-Aventis's teriflunomide, Biogen Idec's BG-12, and Teva/Active Biotech's laquinimod. Despite the convenience of their oral formulations, their efficacy in MS is the key to their market success.

- The most promising emerging agent is FTY-720. With its demonstrated efficacy (which appears superior to that of the IFN-βs and glatiramer acetate [Teva's Copaxone] in Phase II trials thus far), acceptable safety profile, and oral formulation, the drug will garner significant market and patient share following its launch, but it will not outperform all current therapies by 2020 because of concerns over its safety.

- Therapeutic options for CP-MS, which encompasses secondary-progressive MS (SP-MS) and primary-progressive MS (PP-MS), are limited because current therapies do not adequately address the neuronal degeneration characteristic of this type of MS. Two emerging agents are being positioned for this patient population--BioMS Medical's MBP-8298 and rituximab (Biogen Idec/Genentech's Rituxan)--although we do not expect rituximab to launch for this indication.

- Current therapies face patent and exclusivity expiries during our forecast period. To temper the market decline of their branded agents, Bayer Schering Pharma/Berlex, Merck Serono, and Teva are developing follow-on products that are expected to offer comparable or improved efficacy, safety, and tolerability.

- Experts continue to clamor for agents that promote remyelination and/or provide neuroprotection. This prolonged interest in such drugs has prompted extensive research that is slowly translating into clinical trials.

What do the experts say?

Highlights of the expert opinion that informs our analyses:

- At the forefront of the minds of all experts interviewed are concerns over the safety of natalizumab following the development of fatal opportunistic infections in patients taking natalizumab/Avonex combination therapy. These safety concerns have led to restrictions in prescribing and administration of the drug and, in turn, are hurting its market uptake. Experts expect such heightened caution to continue. As one neurologist explains, "Now that it's been re-released with new warnings, there are probably risks we haven't seen yet. I think the use of Tysabri is going to be much, much less than it would have been."

- According to one Spanish expert, "In the future, the most important challenge is safety." Natalizumab's history has made experts acutely sensitive to the potential for severe side effects, and this concern has extended to emerging therapies. Most experts are withholding judgment on emerging therapies until clinical trial data are available. As one U.S. expert explains, "There is still going to be some caution. It's going to depend on the safety during the clinical trial. Even if there aren't any real safety issues that come up during the studies, I'm going to be cautious about using the drug because we don't know what the long-term risks are." Warns a U.K. expert, "Just because the drug gets through all of the very expensive and carefully controlled hurdles, it's no guarantee that it is safe."

- Experts are excited about FTY-720 because, as one expert states, the drug is "probably the most promising and it's the most interesting new mechanism." The drug has demonstrated efficacy in clinical trials and has an oral formulation, but experts are wary of potentially severe side effects. This expert continues, "The only problem is the mechanism of action indicates it blocks lymphocytes from migrating out of the lymph nodes and I think they're going to run into the very same set of problems that they ran into with Tysabri, namely opportunistic infections."

- Oral formulations would provide patients with a more-convenient formulation, a significant advantage in a market of injectables. Although experts acknowledge the advantages of oral therapies, the majority of experts interviewed state that convenience is not the most important driving factor in their treatment decision. Efficacy, then safety, is the most influential factor in choosing an MS treatment, and that attitude is unlikely to change until more information about developing agents is available. As one French neurologist explains, "The problem is safety. With the drugs that have been evaluated in a Phase II study, we have some data about efficacy but not sufficient data about safety."

- Experts overwhelmingly call for agents that promote remyelination or neuroprotection. These agents will be beneficial not only for CP-MS patients, who are underserved by immunomodulatory therapies, but also for early-stage and RR-MS patients. According to one expert, "The neuroprotective component—it's something that we are not doing that

well." Most experts acknowledge that more R&D is required to bring such agents to market.

- Combination use of two immunomodulatory agents has all but ceased following the fatal opportunistic infections that developed with the natalizumab/Avonex combination. "The problem was when you combine two immunomodulatory drugs, you risk having many more side effects because that was a problem [with natalizumab/Avonex use]—there was not enough of an immune system to protect from viral infection," explains one Spanish expert. However, experts admit that combination therapy might still be a possibility. As one Italian expert explains, "Combining neuroprotection with immunosuppression or immunomodulation might well be the future strategy for treating MS."

- The majority of experts interviewed say that current therapies, particularly the IFN-β agents and glatiramer acetate, will continue to sustain the market. Yet, most experts acknowledge that emerging agents will negatively affect the market shares and patient shares of current therapies. A German neurologist states, "I don't know how much money there still is in the beta interferon business because I think they have already reached a ceiling effect. In the future, once other drugs become available, the importance of the interferons will probably be reduced."

What key challenges and opportunities remain?

- Neuroprotection and remyelination are the most significant challenges facing MS treatment, but they offer significant opportunity. Few agents in the pipeline focus on this aspect of MS, yet all MS patients could potentially receive these agents, representing a larger possible drug-treated population than that of any immunomodulatory agent. However, these agents face development hurdles that are not easily overcome, so we do not expect such agents to be available by the end of our study period.

- Current therapies delay disease progression but do not prevent it. Some emerging therapies, particularly FTY-720, may more effectively slow disease progression than the IFN-βs or glatiramer acetate. However, agents that completely halt or even reverse disease progression are still lacking.

- Approximately 35% of MS patients are diagnosed with the chronic-progressive form of the disease, yet drug-treatment rates for this patient population remain low because of the paucity of therapeutic options. We anticipate that only one therapy, BioMS Medical's MBP-8298, will launch for the CP-MS population during our forecast period. However, this therapy promises to be effective only in patients carrying the *HLA-DR2* or *-DR4* gene. As a result, the need for effective therapies for the CP-MS population persists.

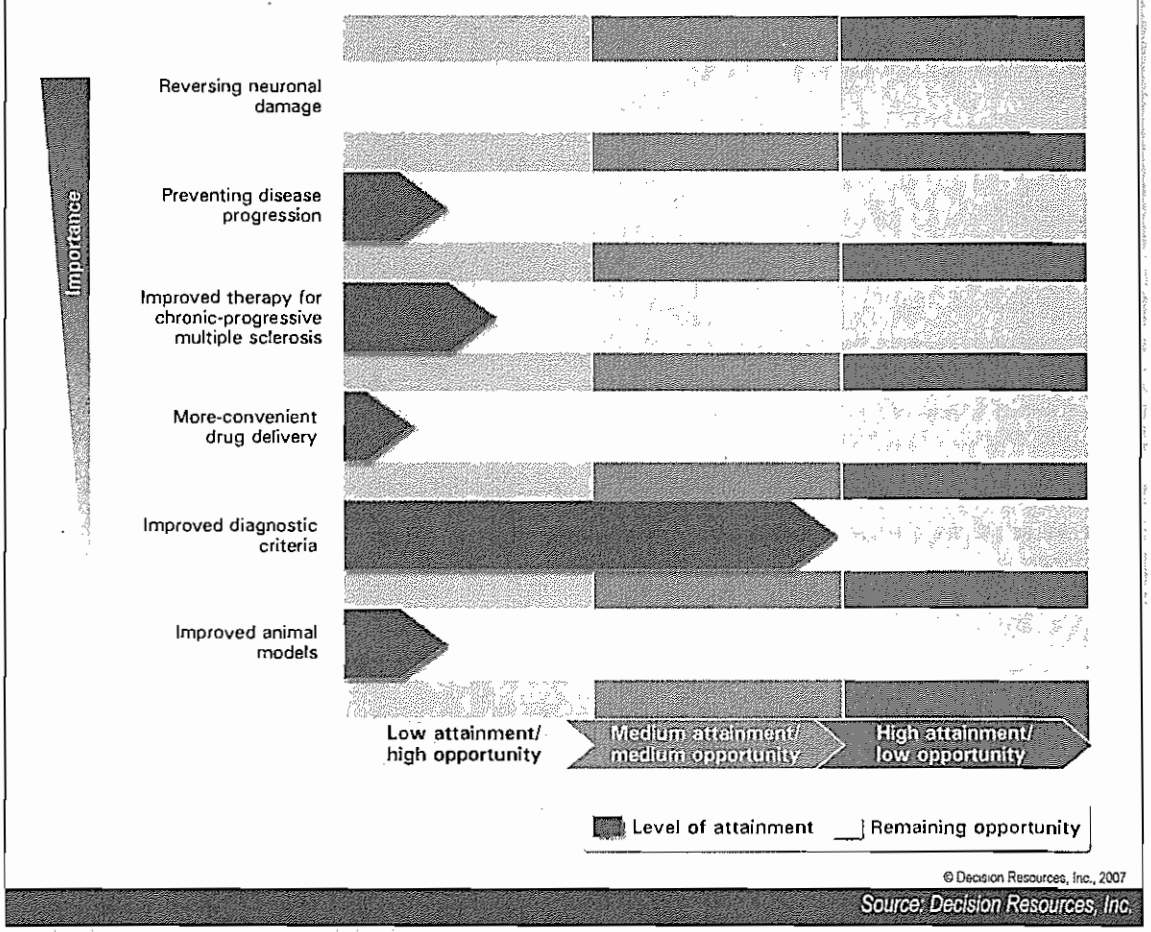
- Early-stage MS, also referred to as clinically isolated syndrome (CIS), has become an approvable indication, and IFN-β agents are expanding their labeling to include this patient population. Nevertheless, because a diagnosis of MS is being made at increasingly early stages of the

disease, the need for safe and efficacious therapies with convenient dosing schedules is growing.

- More-convenient disease-modifying therapies are still needed. In a market of injectables and IV infusions, experts assert that physicians and patients would welcome drugs with oral formulations. In addition, given the chronic nature of MS, agents with less-frequent dosing or improved tolerance would be very advantageous and would likely attain significant market share.

The accompanying figure highlights areas of clinical unmet need—most importantly, the reversal of neuronal damage.

Unmet Needs: Attainment and Remaining Opportunity in Multiple Sclerosis



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Chapter 1

Introduction

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Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
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1. Introduction

Therapies that significantly slow or even halt disease progression continue to be a crucial unmet need in multiple sclerosis (MS). In this report, we forecast the launch of seven novel agents beginning in 2009 that will provide therapeutic options to MS patients underserved by current therapies. Five of these emerging agents are available in oral formulations. The launch of so many oral agents illustrates the drive to meet a significant unmet need in MS. However, to be successful in the MS market, oral formulations must also show clinical efficacy and have at least a modest safety profile.

Indeed, experts tell us, although a drug's efficacy is the primary consideration when prescribing a therapy for MS, the drug's safety profile is of increasing importance to its market success. Experts' wariness surrounding drug safety was prompted by the development of opportunistic infections in three patients (two of which proved fatal) who received natalizumab (Biogen Idec/Elan's Tysabri), launched in the U.S. market in 2004. As a result of overarching concerns about safety and efficacy, we do not forecast that any emerging therapy will obtain blockbuster status during our forecast period. However, some emerging agents, particularly oral therapies, will successfully penetrate the market by 2020; in that year, one-third of the MS therapy market will be attributed to therapies that launch during our forecast period.

Clinicians and patients will enthusiastically welcome oral MS therapies--the formulation and dosing schedule of injectables are onerous to patients. Oral agents will provide much-needed convenience and will likely boost patient compliance and adherence. We anticipate that five oral therapies will launch during our study period: two immunosuppressants and three immunomodulators. Most of these agents will achieve only modest market success because their moderate efficacy and poor safety profiles will limit their use to niche patient populations, for whom these agents will be used in the second- or third-line setting. Novartis/Mitsubishi Pharma's FTY-720 (fingolimod) will outperform other emerging therapies because of its oral formulation, superior efficacy, and acceptable safety profile, although experts temper their excitement by cautioning that severe opportunistic infections may still arise with the use of this drug.

Approximately 35% of MS patients are affected with chronic-progressive forms of MS (CP-MS, which encompasses secondary-progressive and primary-progressive MS), yet these patients have limited therapeutic options because current therapies are not effective in this population. BioMS Medical's MBP-8298 is the only emerging therapy in development for CP-MS that we expect to reach the market during our forecast period, but this agent alone will not adequately address the needs of the CP-MS population. Therapies that promote remyelination or neuroprotection remain a significant unmet need in MS and thus represent considerable commercial opportunity in MS treatment.

Report Coverage

- Outlook by class and compound over an extended 2005-2020 study period.
- Current and emerging drug targets.
- Epidemiology and disease populations.
- Current and emerging therapies, with distinct emphasis on emerging oral immunomodulators, injectable immunomodulators, and neuroprotective/ remyelinating agents.
- Development hurdles and treatment challenges.
- Major markets: United States, France, Germany, Italy, Spain, United Kingdom, and Japan.

Report Features

- Research transparency.
- Primary research.
- Forecast transparency, with full market assumptions.
- Telephone access to analysts for further discussion.

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Chapter 2

Current and Emerging Drug Targets

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Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
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2. Current and Emerging Drug Targets

Key Findings

- Experts and researchers increasingly recognize that MS comprises both autoimmune and neurodegenerative aspects. Still, most therapies continue to target the autoimmune response, leaving few therapeutic options for the approximately 25% of MS patients who do not have an immune component to their disease.
- The most promising emerging agent, Novartis/Mitsubishi Pharma's FTY-720 (fingolimod), targets a novel aspect of T-cell trafficking. Experts are excited but wary about the drug's mechanism of action, fearing it may permit opportunistic infections.
- Research is continually revealing potential drug targets for neuroprotection and remyelination. Whether these targets will yield viable therapies is unclear at this stage.

"MS is a disease of the nervous system. It is not a disease like most autoimmune diseases that affect other organs. So it's hard for me to imagine that just affecting the immune system is going to affect what's going to happen in the nervous system. I think that targeting the nervous system as opposed to targeting the immune system is the way to affect this disease."

—Neurologist, United States

Expert Commentary: Drug Targets in Multiple Sclerosis, 2007

Drug Target	Expert Opinion
The autoimmune attack	"If you come from the premise that the immune system is the problem, then affecting the immune system is going to be effective. But the problem is that we have already tried drugs that affect the immune system. We can't stop MS with these drugs. That tells us the immune system is not very important, that the immune system may not be the primary problem. So, more and more drugs have been developed in that area, and I think they're going to show about the same effect as we're seeing with the present drugs." — Neurologist, United States
T-cell-specific molecules	"In MS we need more new targets to stop the cascade of pathogenesis of the disease. In my opinion, [drugs] that block cytokine IL-12, for instance, are very important and interesting." — Neurologist, France "Because we feel that immunity plays only a part in the disease, the whole story of MS cannot be explained by autoimmunity. I would be very surprised if selective molecules like IL-12 or CD-28 or CD-52, drugs that target these molecules, show to be hugely effective in reducing disability progression." — Neurologist, United Kingdom "Monoclonal antibodies are mainly targeting certain components of the immune system, and, again, I think they are very important, but I doubt that they will really tell us the whole story. They are probably a little more sophisticated than the beta interferons, but in the long run, I don't know whether they will help us to meet the final or the ultimate goal in order to also have an effect on the regeneration and axonal damage." — Neurologist, Germany
T-cell migration	"It's very interesting to use monoclonal antibodies that are able to block the migration of lymphocytes." — Neurologist, France "On the drug development front, FTY-720, the sphingosine phosphate receptor modulator, is probably the most promising and it's the most interesting new mechanism. The only problem is the mechanism of action indicates it blocks lymphocytes from migrating out of the lymph nodes. I think they're going to run into the very same set of problems that they ran into with Tysabri, namely opportunistic infections." — Neurologist, United States
T-cell receptor	"It was shown a long time ago that the immune response at the T-cell receptor level is much too broad for any project targeting the T-cell receptor likely to be useful." — Neurologist, United States
Neuroprotection	"If it's a good drug, it should take care of neuroprotection because we know from the pathogenesis that MS is not only a white matter disease, but from the beginning it also involves the axons. We have to think about neuroprotection." — Neurologist, Italy
Axonal demyelination	"When the axons are denuded, they can be transected and they can be damaged by this inflammatory response. We view the inflammatory response as being more serious from the standpoint of delayed effects on axons rather than the early effects on demyelination." — Neurologist, United States "We have to work out the mechanism of axonal pathology in the disease because they really do not know exactly what happens. Therefore, we have no drug that will target the pathophysiology of this axonal injury." — Neurologist, Germany

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Overview

Multiple selerosis (MS) is an inflammatory disease of the central nervous system (CNS) that is characterized by progressive neurological dysfunction as a result of alterations in the normal function of cells of the CNS. The primary pathophysiological hallmark of MS is the loss of myelin, a layer of lipids and proteins produced by cells called oligodendrocytes that wrap around the neuron and act like an insulating sheath to facilitate electrical conduction along the nerve. The loss of myelin can lead to neuronal degeneration. MS is also characterized by an excess number of astroglial cells, a non-neuronal cell type of the CNS that inereases in number in damaged areas of the CNS (gliosis).

Although MS has several predictable features, such as the involvement of visual, motor, sensory, and autonomic systems, the clinical course of MS varies considerably in individual patients: some patients have benign forms of the disease with remissions lasting for several years, while other patients suffer more aggressive forms of MS from the onset and develop the progressive phase of the disease quickly. In fact, pathophysiological data indicate that there may be several demyelinating diseases collectively referred to as "MS," a finding that explains the vastly different courses of progression seen in patients (Lassmann H, 2001). Physicians interviewed state that more research is necessary to characterize the subcategories of MS and identify a prognostic biomarker capable of differentiating between the different forms of the disease so as to inform their treatment decisions (see Chapter 5, "Development Hurdles and Treatment Challenges," for more information).

Three clinical forms of MS are widely recognized internationally. The most common form of MS, relapsing-remitting MS (RR-MS), is characterized by an immune component of the disease, during which a patient experiences immune system attacks against the myelin sheath (relapse), followed by remission. These relapses are considered the clinical expression of acute inflammatory focal lesions disseminated in the CNS. However, as the myelin sheath around neurons is progressively lost, the immune phase of the disease eventually abates, and the patient progresses to secondary progressive MS (SP-MS), the neurodegenerative phase of the disease, occasionally superimposed with inflammatory relapses. Approximately 85% of patients diagnosed with MS have the relapsing-remitting form (Keegan BM, 2002). An estimated 50% of patients with RR-MS develop SP-MS within ten years, and 90% of patients with RR-MS eventually develop SP-MS (Weinshenker BG, 1989a). Approximately 15% of MS cases begin with an initial course of primary progressive MS (PP-MS). PP-MS patients typically do not experience autoimmune attacks; their disease is degenerative from the onset, a condition that researchers believe reflects the occurrence of axonal loss and gliosis (Confavreux C, 2000). This lack of an immune component to PP-MS explains why these patients do not respond to the immunomodulatory drugs (interferon-betas [IFN-β], glatiramer acetate [Teva's Copaxone]) that are efficacious in RR-MS patients. In this report, we group all MS patients into two categories, RR-MS and chronic-progressive MS (CP-MS, which comprises both SP-MS and PP-MS), based on the practices of experts interviewed.

An additional subgroup that is increasingly being diagnosed is the "early-stage MS" subgroup, or patients with a "clinically isolated syndrome" (CIS). CISs represent isolated demyelinating events (relapses) that may be followed by remission for several years; experts interviewed note that 20-30% of CIS sufferers remain relapse-free five years after a CIS, which explains some neurologists' reluctance to initiate an onerous treatment regimen at this stage. Early-stage MS patients, say thought leaders interviewed, are increasingly diagnosed as the availability of magnetic resonance imaging (MRI) continues to spread, as physicians become more familiar with the McDonald criteria (revised diagnosis criteria that rely on the use of MRI and tend to detect MS at earlier stages), and as patient awareness increases (see Chapter 4, "Current Therapies and Treatment Trends"). Early-stage MS patients are increasingly treated, despite debate in the MS community whether a patient should be treated as soon as early-stage MS is diagnosed or whether treatment should be withheld until a second relapse. This debate stems from reluctance of some patients and physicians to begin a treatment that requires self-injection if the disease follows a benign course and from the reluctance of third-party payers to cover early treatment. One neurologist explains, "If I feel that the patient definitely has MS—and this may be early MS before they even have the temporal change—I will offer treatment. Some patients refuse it initially because they feel great. They've only had one attack and they refuse to go on injection treatment that isn't a cure and might have side effects." Thus, the early-stage MS patient population represents an opportunity for drug developers to expand their drug-treated population. Indeed, IFN-β-1a (Biogen Idec's Avonex, Merck Serono [formerly Serono]/Pfizer's Rebif) and IFN-β-1b (Bayer Schering Pharma [formerly Schering]'s Betaferon/Berlex's Betaseron) are approved in Europe to treat early-stage MS, while Avonex and Betaseron are approved in the United States for this patient population.

Not surprisingly, given the clinical differences underlying the two types of MS, therapies that show efficacy in treating the autoimmune/inflammatory aspect of MS (as seen in RR-MS patients) do not demonstrate any efficacy in treating the degenerative component (as seen in CP-MS patients) unless the progressive form also has an inflammatory component, as it does in SP-MS patients who relapse. RR-MS patients and SP-MS patients (particularly those experiencing relapses) are currently treated with drugs designed to dampen immune attaeks. However, no drugs are available to prevent neuronal damage, and experts interviewed clamor for such a therapy. A drug that demonstrates efficacy in slowing or preventing neurodegeneration would be a major achievement in the treatment of MS and would likely be prescribed as first-line therapy in all MS patients because even patients with very early RR-MS show signs of neurodegeneration (Kuhlmann T, 2002; Rovaris M, 2005).

In the following section, we detail the functions of individual components of the immune system that are involved in the episodic autoimmune attacks characteristic of RR-MS.

Unlike RR-MS patients, patients with CP-MS are not affected by periodic inflammatory attacks on myelin. The hallmark of CP-MS is demyelination and degeneration of CNS neurons, an effect that leads to increasing disability. Once enough myelin has been destroyed by the immune system attacks (demyelination), neurons that used to be covered and protected by myelin,

much like a wire wrapped in an insulating sheath, begin to die in a process called degeneration. We discuss this process in greater detail in the section "Demyelination."

The Autoimmune Attack in Multiple Sclerosis

In MS, myelin is the target of an autoimmune attack, a complex inflammatory reaction against the natural molecules in a patient's body (self-antigens) that destroys the myelin and leaves behind well-demarcated hypocellular areas—that is, areas with lower-than-normal counts of myelin-forming oligodendrocytes. These hypocellular areas are called plaques. The immune attack involves helper T cells, B cells, and the complement cascade. Chemokines, small proteins secreted by T cells, amplify the immune reaction by attracting additional T cells to the site of inflammation; in MS, chemokines attract T cells across the blood-brain barrier (BBB) into the CNS. Once in the CNS, T cells secrete proinflammatory cytokines that amplify the immune system attack on myelin, as do microglia and astrocytes, two non-neuronal cell types found in the CNS. Anti-inflammatory therapies target various components of the autoimmune attack; therefore, these therapies can help only patients who are suffering relapses—that is, RR-MS patients and patients who have progressed to SP-MS but are still relapsing.

In the following sections, we describe the roles of the individual immune components. Figure 2-1 illustrates these components and the sequence of events presumed to be the pathophysiologieal course of MS.

T Cells

Most researchers agree that the autoimmune activity in MS primarily involves a specific type of T cell called T-helper (T_H, or $CD4^+$ T cells) cells, although cytotoxic T cells (or $CD8^+$ T cells) also proliferate in MS and experimental allergic encephalomyelitis (EAE) lesions, a rodent disease model for MS (D'Souza SD, 1996; Huseby ES, 2001; Sun D, 2001). As part of the initiation of an immune attack, naive Th cells (or T_H0) cells undergo activation, develop into specific subsets of T cells, and then migrate to the site of inflammation (see the detailed sections that follow).

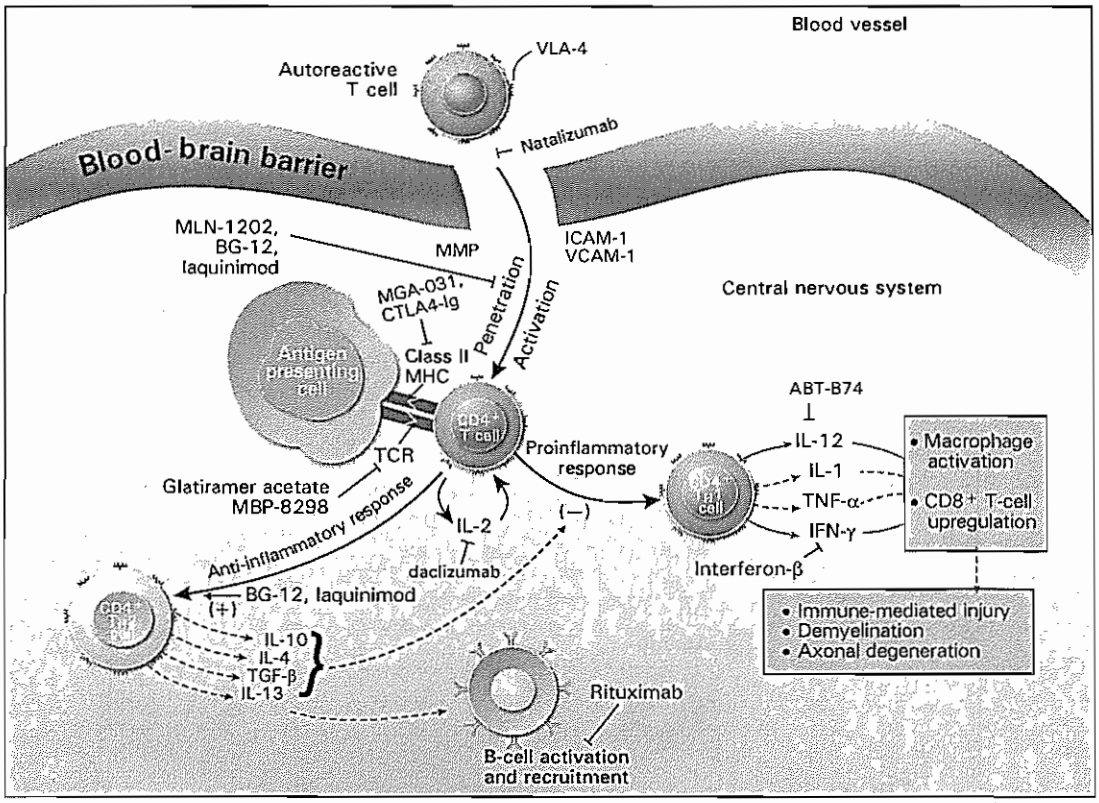
T-Cell Activation

Naive T_H cells are activated when the T-cell receptor (TCR) expressed on the T-cell surfaee recognizes a specific antigen bound to a major histocompatibility complex (MHC) molecule located on the surface of an antigen-presenting eell (APC). For the T cell to become active and proliferate, the APC must provide a costimulatory signal to the naive T cell; this costimulatory signal is initiated by the B7 protein on the APC surface, which binds to the CD28 protein on the T-cell surface (Figure 2-2). Upon receiving the antigen-speeific signal and the costimulation signal, the activated T cell begins to divide and proliferate in a process known as clonal expansion.

Several therapeutic strategies in MS target the process of clonal expansion, including nonspecific chemotherapeutic agents and specific targets of T-cell clonal expansion (see Chapter 6, "Emerging Oral Immunomodulatory Therapies"). Immunosuppressive agents, such as mitoxantrone (Merck

Figure 2-1

Multiple Sclerosis Immune Pathophysiology



Myelin is the target of a cascade of events in the pathology of multiple sclerosis (MS).

In MS, demyelination of neurons and oligodendrocytes is the disease hallmark. Axons become denuded and excitatory nerve transmission is compromised. Often, neurons become axotomized, resulting in permanent neurological deficits. The immune attack on myelin is mediated by autoreactive T cells that respond to genetic and/or environmental factors and move from the systemic circulation into the central nervous system (CNS). Some disruption of the blood-brain barrier (BBB) must occur for the autoreactive T cells to penetrate the CNS; matrix metalloproteinases (MMP), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) may play a role in disrupting the BBB. Interaction with antigen-presenting cells (via the major histocompatibility complex, [MHC], and T-cell receptor [TCR]) activates the T cell and stimulates the formation of T-helper cell-1 (T_H1). T_H1 cells secrete proinflammatory cytokines and factors such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), and interleukin 12 (IL-12). These cytokines in turn activate macrophages and another group of T cells ($CD8^+$). Autoreactive T cells are also transformed into another population of T-helper cell-2 (T_H2). T_H2 cells secrete a separate repertoire of cytokines (IL-10, IL-4, transforming growth factor-beta, [TGF-β], and IL-13). Most of the T_H2 secreted cytokines act to curb the inflammatory response, with the exception of IL-13 (involved in B-cell recruitment), which may play a role in the inflammatory process.

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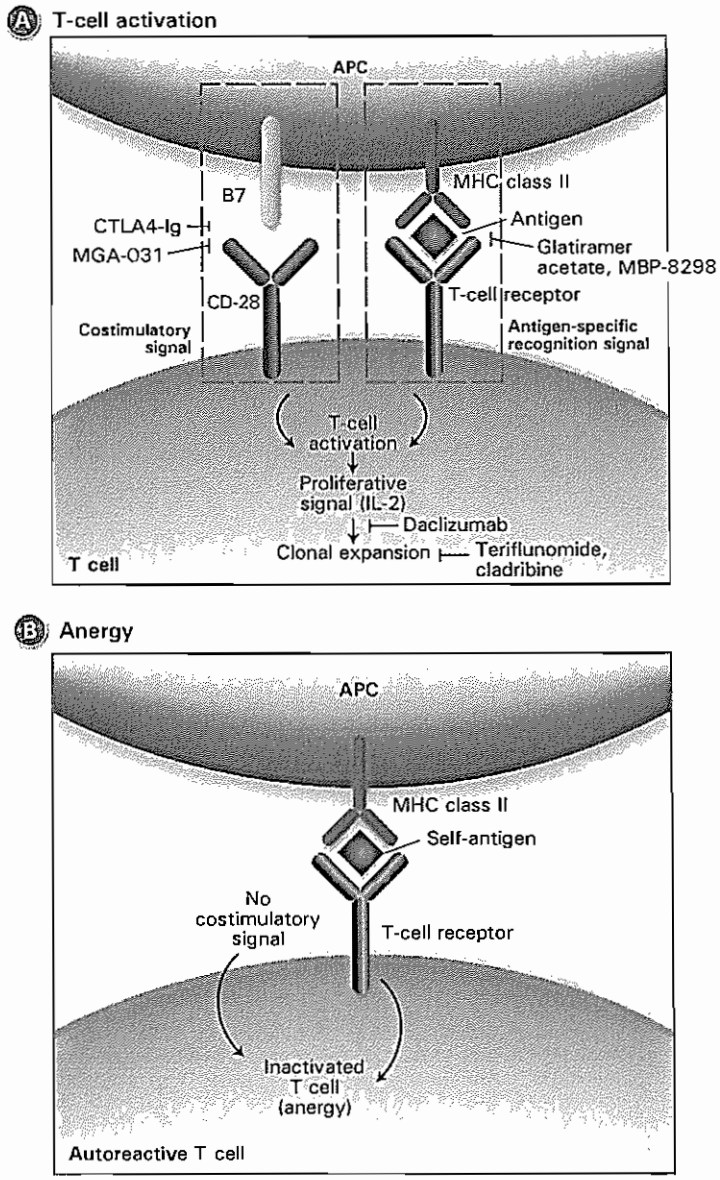
Source: Decision Resources, Inc.

Figure 2-2

Two Independent Signals in T-Cell Activation



APC = Antigen-presenting cell; CTLA4 = Cytotoxic T-lymphocyte-associated protein 4; Ig = Immunoglobulin; IL = Interleukin; MHC = Major histocompatibility complex.

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Serono/Amgen's Novantrone), Sanofi-Aventis's teriflunomide, and Merck Serono's oral cladribine (Mylinax), target rapidly dividing cells nonspecifically. In addition to arresting clonal expansion of activated T cells, chemotherapeutic agents target all cell division, including normally dividing cells; as a result, these agents have a poor safety profile and are used only for particularly aggressive forms of RR-MS and SP-MS. Another therapy that specifically targets the division of activated T cells is the monoclonal antibody (MAb) daclizumab (PDL BioPharma/Biogen Idec; Roche's Zenapax, marketed for control of kidney transplant rejection); it is directed against the cytokine interleukin-2 (IL-2). IL-2 is secreted by T cells upon receiving the costimulatory signal from the B7/CD28 protein interaction and drives the clonal expansion of activated T cells. Thus, daclizumab may arrest the clonal expansion of autoreactive T cells upon their activation by the B7/CD28 interaction. However, physicians interviewed caution that therapeutic strategies that target such broad immunosuppression as arresting clonal expansion of the immune system may allow the development of opportunistic infections in treated patients.

A novel therapeutic target that has emerged is the protein osteopontin, which has roles in bone formation, inflammation, and cancer (Denhardt DT, 2001). Large-scale genetic screens have identified differential expression patterns of genes, including that of osteopontin, in the neurons of MS patients compared with the gene expression pattern of healthy persons (Chabas D, 2001). In the EAE mouse model, osteopontin promoted survival of activated T cells and worsening neurological deficits (Hur EM, 2007), suggesting that osteopontin is a viable therapeutic target in MS. Indeed, Merck Serono and Astellas (under license from Immuno-Biological) are each conducting preclinical studies of osteopontin in MS.

T_H1 and T_H2 Cells

Some activated T_H cells develop into subsets of T cells, known as T_H1 and T_H2 cells, by mechanisms that are still incompletely understood but appear to depend on the composition of cytokines present in the T cell's environment. T_H1 cells secrete proinflammatory cytokines that amplify the immune response. T_H2 cells secrete anti-inflammatory cytokines that reduce the immune response.

Presumably, proinflammatory cytokines secreted by T_H1 cells (e.g., interferon-gamma [IFN-γ] and interleukin-12 [IL-12]) cause inflammation of the CNS tissue and contribute to demyelination and disease progression in MS, while T_H2 cells secrete anti-inflammatory cytokines (e.g., transforming growth factor-beta [TGF-β], IL-4, IL-10) that retard the progression of MS (see Figure 2-1). Abbott Laboratories' ABT-874 (see Chapter 7, "Emerging Injectable Immunomodulatory Therapies") is a MAb directed against the IL-12 cytokine that may inhibit IL-12-induced T-cell activation, thus dampening the severity of an autoimmune attack. Physicians interviewed caution that, similar to agents targeting T-cell clonal expansion, this therapeutic approach may be too nonspecific for the treatment of MS.

IFN-β, the most frequently prescribed therapy for RR-MS patients, is another anti-inflammatory cytokine; it halts the progression of MS by inhibiting the proinflammatory IFN-γ cytokine and stimulating the production of the anti-

inflammatory IL-10 cytokine. Clinical studies have shown that IFN-β therapy can cause a 30% decline in disease progression; use of IFN-β therapy in the treatment of MS is discussed in Chapter 4, "Current Therapies and Treatment Trends." Interferons continue to be in development as potential therapies for MS; for instance, an oral interferon, Pepgen's interferon-tau (Tauferon), is in development and is thought to function similarly to IFN-β therapies. Despite the continued interest in interferons as MS therapies, experts interviewed are skeptical about the success of oral interferons because of their poor bioavailability.

Other therapies in development for MS appear to shift T-cell cytokine production from proinflammatory cytokines (T_H1) to anti-inflammatory cytokines (T_H2). The oral immunomodulators BG-12 (Biogen Idec) and laquinimod (Teva/Active Biotech's SAIK-MS), as well as the statin simvastatin (Merck & Co.'s Zocor), are believed to induce a change in the cytokine profile in favor of anti-inflammatory cytokines (T_H2), although their exact mechanism of action is unclear (see Chapter 6, "Emerging Oral Immunomodulatory Therapies").

T-Cell Self-Recognition and the Autoimmune Response in Multiple Sclerosis

The aforementioned requirement that the APC deliver both the antigen-specific and costimulatory signals is critical to preventing an autoimmune reaction against self-antigens. Most naive T cells that target self-antigens (autoreactive T cells) receive only the antigen-specific signal (mediated via the TCR-MHC-antigen complex). Without the B7/CD28 costimulatory signal, the autoreactive T cell does not become activated; instead, it becomes refractory to later stimulation by an antigen, a state known as *anergy*—the T cell is, in effect, turned off and unable to initiate an autoimmune response (see Figure 2-2).

Several companies are exploring the process of T-cell activation as a target for MS (see Chapter 7, "Emerging Injectable Immunomodulatory Therapies"). Bristol-Myers Squibb recently launched CTLA4-Ig (abatacept, Orencia), a protein engineered to block the B7/CD28 costimulatory signal, for the treatment of rheumatoid arthritis (RA) and it is investigating the drug's potential in MS. Inhibition of the costimulatory signal may prevent activation of naive autoreactive T cells. MacroGenics is investigating antigen recognition as a therapeutic target in MS. The company's humanized MAb MGA-031 (teplizumab) binds to the CD3 signaling side chain of the TCR and interferes with the signaling process upon binding of the self-antigen to the TCR. Although it is still unclear how MGA-031 targets autoimmune T cells, without the proper signaling to the T cell upon self-antigen/APC binding to the TCR, T cells will not be activated and the autoimmune mechanism underlying MS will be halted.

Naive autoreactive T cells must encounter a self-antigen to undergo anergy; if not, they can still be activated by a self-antigen on an APC and initiate an autoimmune reaction. A naive autoreactive T cell could remain sequestered from a self-antigen if the self-antigen is present in a region of the body to which T cells do not typically have access. One such immunoprivileged area is the CNS; the BBB normally isolates the CNS from T cells in circulation.

If autoreactive T cells are able to invade the CNS, an immune reaction still will not occur because (1) the self-antigen is not presented to the T cell by an APC and (2) a class of T cells known as "regulatory T cells" prevents these T cells from being activated via mechanisms that are still unclear.

Most autoreactive T cells are deleted during normal T-cell development, although some naive autoreactive T cells survive in an adult organism, held in check by regulatory T cells. One novel approach to MS therapy is to target regulatory T cells; activation of these cells will likely reduce the number of autoreactive T cells and therefore the immune response. Immune Response Corporation is developing NeuroVax, a vaccine that targets TCRs specific to myelin basic protein (MBP), one of the proteins found in highest abundance in the myelin sheath. By activating regulatory T cells, this vaccine will deplete pathogenic MBP-specific T cells (see Chapter 7, "Emerging Injectable Immunomodulatory Therapies"). However, experts interviewed caution that such an approach will not completely eliminate activated T cells because T cells recognizing other self-antigens will remain unaffected by NeuroVax.

Interestingly, a recent study demonstrated that the generation of regulatory T cells may be mediated in part by neurons themselves (Liu Y, 2006). Researchers demonstrated that interactions between T cells and neurons in the CNS, together with growth factors secreted by neurons, promote the conversion of pathogenic T cells into regulatory T cells. These regulatory T cells will in turn suppress other pathogenic T cells, dampening the extent of the immune response.

T-Cell Migration and Entry into the Central Nervous System

Following activation in secondary lymphoid organs, T cells must exit the lymphoid organs to migrate to the site of inflammation. T-cell exit from lymphoid organs requires the presence of the sphingosine-1-phosphate (S1P) receptor on their cell surface; FTY-720 (Novartis/Mitsubishi Pharma's fingolimod, see Chapter 6, "Emerging Oral Immunomodulatory Therapies") is an immunosuppressive drug that acts as an S1P receptor agonist. S1P receptors are internalized upon binding to FTY-720, reducing the number of active S1P receptors on the T cell's surface. Consequently, T cells are unable to migrate out of the lymphoid organs to initiate an immune response. Physicians interviewed caution, however, that such a general immunosuppressive mechanism may allow the development of opportunistic infections because activated T cells would be unable to combat an opportunistic infection that may arise, similar to the effect seen in patients treated with natalizumab (Biogen Idec/Elan's Tysabri), discussed later in this chapter.

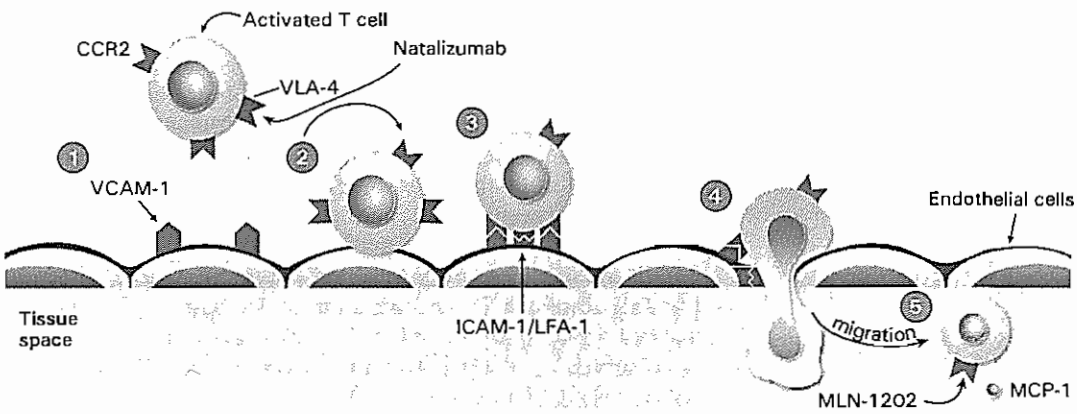
T cells migrate from the secondary lymphoid organs via the blood to the site of inflammation; this migration to the proper location is controlled by a number of factors, including chemokines (discussed in detail in a later section), and requires T-cell expression of molecular mediators. One agent in development targeting T-cell recruitment is Marnac's pirfenidone, an inhibitor of p38 MAP kinase; this enzyme is critical for T-cell recruitment, so its inhibition will potentially prevent proper T-cell targeting to the site of inflammation.

T cells enter the CNS through endothelial cells lining the cerebral blood vessel walls, which express the vascular cell adhesion molecule (VCAM-1) in response to proinflammatory cytokines. Simultaneously, activated T_H1 cells begin expressing the very late antigen-4 (VLA-4) protein on their cell surfaces. The VLA-4 protein binds to VCAM-1 on vessel endothelial cells; this interaction allows T_H1 cells to migrate through the vessel lining into the CNS (Figure 2-3).

The MAb natalizumab (see Chapter 4, "Current Therapies and Treatment Trends") targets the VLA-4 protein to block the interaction between VLA-4 and VCAM-1, thereby preventing activated T-cell migration into the CNS (Figure 2-3). This therapeutic strategy has the potential to allow opportunistic infections to develop. Indeed, three MS patients and two Crohn's disease patients treated with natalizumab developed progressive multifocal leukoencephalopathy (PML), an often fatal disease that is the result of CNS infection by the JC virus. The infections developed into PML because patients' T cells were prevented from entering the CNS to fight the infection, and three of these five patients died. The FDA consequently placed a hold on clinical programs targeting VLA-4 receptors until their safety risks could be assessed. Because of these events, patient and physician awareness of opportunistic infections associated with MS therapies has increased dramatically.

Figure 2-3

Migration of Activated T Cells into the Central Nervous System



(1) The expression of various CAMs (i.e., selectins and VCAM-1) is upregulated in the presence of proinflammatory cytokines such as TNF-α and IL-1. (2) Early weak adhesion, or "rolling," is caused by the low affinity binding of selectins to their ligands. (3) The binding of VLA-4 to VCAM-1 and ICAM-1 to its ligands causes firm adhesion of the T cell to the epithelial cells and initiates the secretion of various chemokines and (4) the migration of the T cell across the endothelial layer (diapedesis). (5) The T cell then migrates to the site of inflammation, which is directed by the binding of chemokines such as MCP-1 to their chemokine receptors (i.e., CCR2).

CAM = Cell adhesion molecule; CCR2 = Chemokine receptor-2; ICAM-1 = Intercellular adhesion molecule-1; IL-1 = Interleukin-1; LFA-1 = Lymphocyte function-associated antigen-1; MCP-1 = Monocyte chemoattractant protein-1; TNF-α = Tumor necrosis factor-alpha; VCAM-1 = Vascular cell adhesion molecule-1; VLA-4 = Very late antigen-4.

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Source: Decision Resources, Inc.

Despite the concerns surrounding opportunistic infections, VLA-4 continues to be investigated as a therapeutic target. GlaxoSmithKline and Tanabe are collaborating on an oral VLA-4-antagonist, SB-683699/T-0047, for potential treatment of MS (see Chapter 7, "Emerging Injectable Immunomodulatory Therapies"). Several other companies are pursing development programs that target the VLA-4/VCAM-1 interaction, including Isis Pharmaceuticals, UCB/ Biogen Idec, Roche, and Encysive Pharmaceuticals.

Other cell adhesion molecules that have been implicated in MS—the E-, L-, and P-selectins, the integrin leukocyte function antigen (LFA-1), and other immunoglobulin family members (e.g., ICAM-2, V-CAM, LFA-3, PECAM-1, Mac-1)—may serve as targets for MS therapy; however, as with the VLA-4 antagonists, these targets present a risk of opportunistic infections.

Cerebral blood vessel walls are composed of the protein collagen, which must be digested for T cells to migrate into the CNS. Matrix metalloproteinases (MMPs) are proteins secreted by T cells that digest the collagen, allowing T cells to pass into the CNS. IFN-β therapies used in MS inhibit MMP activity, in addition to inhibiting proinflammatory cytokines, and thus prevent T-cell migration into the CNS (Yushchenko M, 2003). Merck Serono is investigating an oral MMP-12 inhibitor for MS; its goal is to prevent activated T cells from infiltrating the BBB and passing into the CNS.

Other therapies in development for MS are thought to reduce T-cell infiltration, but their exact mechanism of action in altering T-cell infiltration is unclear. Preclinical studies have demonstrated that BG-12, laquinimod, and simvastatin reduce T-cell infiltration into the CNS, in addition to their potential role in shifting the cytokine profile (see Chapter 6, "Emerging Oral Immunomodulatory Therapies").

The T-Cell-Mediated Inflammatory Reaction in the Central Nervous System

Once myelin-specific T cells migrate into the CNS, they can encounter astrocytes and microglia, the APCs of the CNS. These cells, which eliminate cellular debris under normal circumstances, are capable of presenting myelin protein fragments to autoreactive T cells, which then become activated and attack the myelin sheath. Circulating, naive, autoreactive T cells are thought to become activated in MS because of a viral or bacterial infection. Some viral proteins have chemical structures similar to structures of myelin proteins, and it is thought that infections of such viruses activate T cells that recognize self-myelin proteins. The myelin proteins recognized by T cells are thought to include MBP, myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), myelin proteolipid protein (PLP), alpha B-crystallin, phosphodiesterases, and S-100 protein (Noseworthy JH, 2000). T cells specific for MOG, MBP, or PLP can induce EAE in rodents.

Microglia and astrocytes also contribute to myelin destruction by releasing cytokines and other inflammatory mediators, such as free radicals and glutamate, which sustains or worsens the destructive autoimmune reaction within the CNS. The secretion of the cytokine IFN-γ by activated T_H1 cells has several consequences that further exacerbate inflammation in the CNS.

First, IFN-γ induces the expression of MHC proteins on APCs in the CNS; a final therapeutic action of IFN-β entails the antagonism of MHC receptor expression driven by IFN-γ. Second, IFN-γ induces the secretion of MMPs and other proteases (enzymes that degrade proteins into peptide fragments) by microglial cells; these proteases degrade myelin proteins, which are then presented by APCs to myelin-specific T cells. When these T cells become activated, they in turn secrete more IFN-γ, thereby worsening the inflammatory response.

One therapeutic strategy attempted in treating MS is to block the TCR-MHC-myelin protein fragment complex by forcing TCRs to bind altered peptide ligands (APLs). These APLs resemble the structure of myelin protein fragments closely enough to bind TCRs directed against myelin proteins, but they are sufficiently different from natural myelin protein fragments to prevent activation of T cells. Glatiramer acetate is one such APL therapy. Both Teva and BioMS Medical are developing APLs: TV-5010 and MBP-8298, respectively (see Chapter 7, "Emerging Injectable Immunomodulatory Therapies"). MBP-8298 is in development primarily for the SP-MS population and appears to be effective in the population of patients also expressing the human leukocyte antigen *HLA-DR2* and *HLA-DR4* genes.

A novel therapeutic approach in MS is to actively deplete T cells that are specific for myelin proteins; depletion of these pathogenic T cells will reduce the inflammatory response and subsequent myelin destruction associated with MS relapses. The T-cell vaccine Tovaxin, in development by Opexa Therapeutics, targets T cells specific for three myelin proteins: MBP, MOG, and PLP (see Chapter 7, "Emerging Injectable Immunomodulatory Therapies"). Antibodies directed against MBP and MOG have been detected in CNS samples harvested from EAE rodents and from human MS lesions (Raine CS, 1999). Another vaccine, BHT-3009, is in development by Bayhill Therapeutics. This agent is a DNA sequence that encodes MBP, which, when introduced into MS patients, is thought to produce MBP that will compete with endogenous MBP. T cells that are specific to MBP are thought to bind to the MBP produced by the drug instead of endogenous MBP. Because the artificial MBP is not presented by an APC, the artificial MBP/TCR interaction will not provide the costimulatory signal necessary for activation of T cells and these cells will undergo anergy and thus reduce the inflammatory response associated with MBP-specific T cells (see Chapter 7, "Emerging Injectable Immunomodulatory Therapies").

B Cells

Once the BBB is rendered permeable by the action of MMPs, B cells can infiltrate the CNS. They can either act as APCs, thereby furthering the immune response, or secrete antibodies, including immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM). Biogen Idec and Genentech are developing a MAb called rituximab (Rituxan, see Chapter 7, "Emerging Injectable Immunomodulatory Therapies"), which is designed to prevent B-cell activation and consequent antibody secretion for MS. Rituximab binds the CD20 receptor on the surface of B cells, an action that signals macrophages to eliminate the rituximab-bound B cells.

Similarly, Bayer Schering Pharma and Genzyme are codeveloping alemtuzumab (Campath; see Chapter 7, "Emerging Injectable Immunomodulatory Therapies"), an antibody directed against the CD52 protein present on all lymphocytes (B and T cells), macrophages, and monocytes. Binding of the MAb to the cell surface initiates a cascade of events, culminating in cell death. Because alemtuzumab is specific for CD52, it can deplete the disease-causing activated lymphocytes but spare lymphocyte precursors, which do not express CD52 until later in development. By targeting and depleting lymphocytes, developers hope that the agent will halt or slow the inflammatory process that leads to MS disease progression. The companies, however, suspended dosing of the drug in a Phase II trial in September 2005 following three cases of secondary idiopathic thrombocytopenic purpura (ITP) in MS patients. Despite these safety concerns, Phase III trials are slated to begin in early 2007.

Antibodies in Multiple Sclerosis

One of the hallmarks of MS is a higher-than-normal amount of IgG in the cerebrospinal fluid (CSF), indicating the presence of an inflammatory response in the CNS; some IgA- and IgM-containing cells have also been found in actively demyelinating MS lesions. Patients with MS demonstrate a greater variety of antibodies in their CSF than do healthy people, and the antibodies are more numerous in patients who have had MS for a long time. However, antibodies in CSF are found in indications other than MS, including meningitis, encephalitis, syphilis, and idiopathic polyneuropathies. In addition, antibodies are absent in approximately 10% of MS patients, so their role in MS is difficult to ascertain.

Complement Cascade

Antibodies activate the destructive complement cascade. The terminal product of the complement cascade, known as the membrane attack complex, is critical to demyelination and is detected in actively demyelinating lesions (Mead RJ, 2002; Prineas JW, 2001). Membrane attack complexes are believed to destroy oligodendrocytes, the cells that form myelin, by binding directly to the myelin surface and creating holes in its membrane (opsonization). Currently, no therapy to antagonize this arm of the immune system is in clinical development for MS.

Chemokines

Chemokines are chemical signals that are instrumental in attracting T and B cells from the circulatory system across the BBB and into the CNS. Individual chemokines selectively attract particular populations of immune cells by binding to chemokine receptors on the surfaces of T and B cells. Therapies that target these chemokines potentially offer highly specific therapy for MS.

Several companies are vigorously pursuing chemokine receptors as potential drug targets for MS. Millennium is developing the chemokine receptor-2 (CCR2) antagonist MLN-1202 (see Chapter 7, "Emerging Injectable Immunomodulatory Therapies"). ChemoCentryx and Advance Immuni T are developing CCR2 and CCR5 inhibitor programs, respectively, although little

information about these programs is available. Drug developers hope that chemokine receptor antagonists will prevent T cells and B cells from binding to chemokines and being attracted to the site of the immune attacks in MS patients (myelin), thus preventing the worsening of the attacks.

Demyelination

Noxious chemicals precipitated by the autoimmune attack—including certain cytokines, glutamate, proteases, and free radicals—penetrate and ultimately destroy oligodendrocytes, the cells responsible for production of the myelin sheath. The loss of myelin that accompanies destruction of oligodendrocytes, termed *demyelination,* eventually strips bare sections of axonal fibers, thereby creating lesions, or plaques, in the brain or spinal cord (Figure 2-4). The lesions slow, scramble, or interrupt electrical transmission along nerves, especially nerves that serve vision, sensation, and use of the limbs. With disease progression, the number of plaques increases; eventually, with little myelin remaining to be destroyed, the immune attack subsides. As MS progresses, demyelination may be accompanied by axotomy—that is, axons degenerate to the point that they are physically cut in half, and the transmission of electrical signals along the nerve is irreversibly interrupted, which manifests clinically as neurological disability (e.g., impaired mobility, spasticity, tremors [see Figure 2-4]). As neurons progressively die, neurological damage accumulates, and this axonal loss is associated with the permanent disability characteristic of the progressive forms of the disease (Kieseier BC, 2003).

No therapies aimed at protecting the neurons have yet reached advanced stages of clinical development. Experts interviewed state that such a therapy would be beneficial to both RR-MS and CP-MS patients because neuroprotective agents would delay disability progression in all patients regardless of their MS subtype (inflammatory or progressive). Experts interviewed stress that neuroprotective agents will be welcomed most by CP-MS patients, who have few therapeutic options; the treatment of these patients therefore presents a large area of unmet need and commercial opportunity.

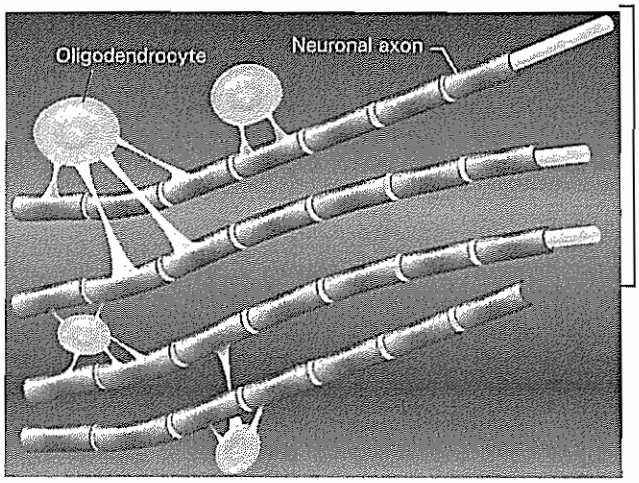
Inhibition of Remyelination

Axon remyelination is a therapeutic goal, and although many potential therapies arise in the laboratory, few agents show clinical utility in humans. Remyelination requires a complex interaction of numerous factors and involves multiple cell types—oligodendrocytes, astrocytes, neurons—and the specific interplay of these components in vivo is much more intricate than what is often demonstrated by in vitro studies.

Remyelination is inhibited in part by astrocytes migrating into the lesion site (gliosis), an event that may mark the transition to the degenerative form of MS (Compston A, 2002), yet recent data suggest that astrocytes may also play a neuroprotective role. Astrocytes produce the cytokine IL-11, which promotes oligodendrocyte survival and maturation in cultures, as well as myelin production; IL-11 is present in MS plaques, suggesting that this factor promotes remyelination (Zhang Y, 2006).

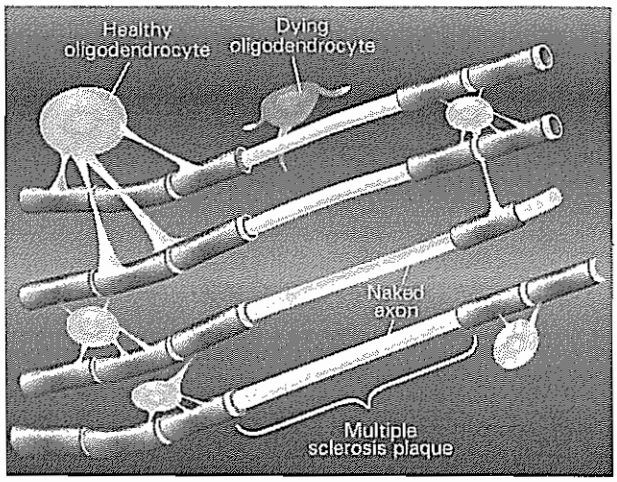
Figure 2-4

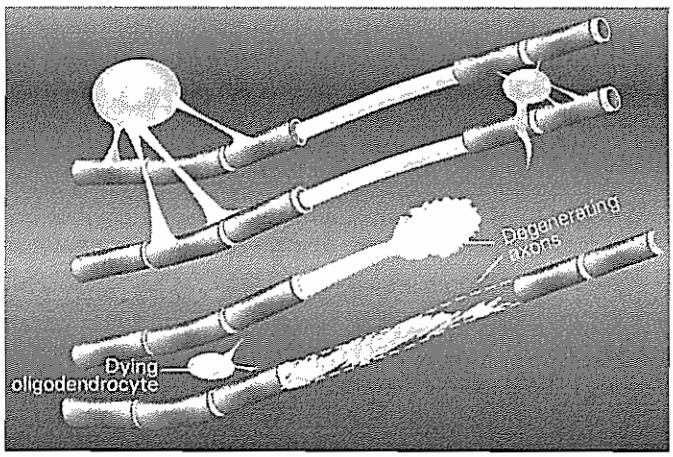
Demyelinating Plaques in Multiple Sclerosis



A. Central nervous system myelin is formed by oligodendrocytes wrapping around the axon like an insulating sheath around a copper wire.

B. Demyelinated regions of a neuronal tract are referred to as "plaque."





C. Extensive demyelination may lead to degeneration of axons, resulting in clinical disability.

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Oligodendrocyte growth and differentiation, which are essential for remyelination, are mediated by a variety of growth factors, including glial growth factor (GGF), insulin-like growth factor-1 (IGF-1), and IL-11; such factors represent potential therapeutic targets for MS. Acorda Therapeutics' recombinant human glial growth factor-2 (rhGGF2) is the only remyelinating agent in development for MS (see Chapter 8, "Emerging Neuroprotective and Remyelinating Therapies"). Although clinical data are lacking, preclinical studies demonstrate that in EAE, rhGGF2 promotes remyelination; this treatment has also been shown to improve relapse rates (Cannella B, 1998; Marchionni MA, 1999).

Signaling factors required for remyelination represent potential therapeutic targets in MS. One such signaling molecule is the receptor protein Notch-1. Notch-1 signaling regulates cell proliferation and differentiation. In EAE, Notch-1 is expressed at high levels by oligodendrocytes and astrocytes in remyelinating lesions but is expressed at low levels in demyelinating lesions (Seifert T, 2006), suggesting that increased Notch-1 signaling may promote remyelination. However, given that additional factors and signaling pathways are involved in myelin production (including Notch-1's natural targets), it is unlikely that modifying Notch-1 signaling will induce complete remyelination.

Another exciting potential therapeutic target for remyelination is the Lingo-1 protein, the first myelination-inhibitory protein thoroughly characterized thus far. Activated Lingo-1 expressed by oligodendrocytes and neuronal axons prevents differentiation of oligodendrocytes and subsequent myelination of neurons (Lee X, 2007; Mi S, 2005). Researchers at Biogen Idec reported that inhibition of Lingo-1 signaling permits oligodendrocytes to myelinate axons in cultures, suggesting that remyelination of neurons could be achieved in MS patients once Lingo-1 signaling is prevented. Although Lingo-1 is an important target based on in vitro results, several other myelination inhibitory factors are likely present in vivo that would need to be neutralized in a localized fashion.

Axonal Degeneration and Neuronal Cell Death

Axonal degeneration in MS is likely a consequence of consistent demyelination; indeed, physiologically severed axons are the pathological correlate of irreversible neurological impairment in MS (Trapp BD, 1998). Interestingly, MRI evidence suggests that recovery from relapses may be the result of the reassignment of neurons in the cortex to innervate regions damaged by MS lesions (Rocca MA, 2003). Based on this evidence, SP-MS would then develop when the degree of lesion injury outweighs the adaptive response of the CNS. Kuhlmann and colleagues have demonstrated that, paradoxically, axonal damage is most severe during the first year of the disease, whereas axon loss is reduced in lesions from patients diagnosed with MS for more than a decade, a finding that suggests that initial axonal damage is more rapid than subsequent damage (Kuhlmann T, 2002).

Neuronal cell death in EAE and MS is mediated in part by the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) protein. When researchers blocked TRAIL's activation in an EAE model, they found that neuronal

apoptosis was reduced in the brain stem motor areas of these animals (Aktas O, 2005). Importantly, clinical disability scores improved in these animals, suggesting that selectively blocking TRAIL signaling in the CNS of MS patients may improve their clinical outcome.

One novel strategy for MS therapy targets the regulation of cell death by modulating neuronal signaling. The alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate acid (AMPA) receptor binds the excitatory neurotransmitter glutamate, which is found at high levels in MS (Steinman L, 2000). Binding of glutamate to AMPA receptors alters ion concentrations (Na^+, Ca^{2+} and Cl^-) in the cell. Overstimulation of AMPA receptors severely disrupts normal ion concentrations, resulting in a series of cellular changes (excitotoxicity) that lead to cell death. Eisai's E-2007 is an AMPA receptor antagonist that may protect oligodendrocytes and neurons by inhibiting excitotoxicity-mediated cell death; in EAE, E-2007 reduced axonal damage and demyelination (Yamauchi T, 2002)(see Chapter 8, "Emerging Neuroprotective and Remyelinating Therapies").

A therapeutic strategy that some physicians view with enthusiasm consists of introducing oligodendrocyte progenitor cells into the CNS and inducing their differentiation so that they can remyelinate neurons that have been demyelinated by an immune attack. This stem-cell therapy approach is a distant goal, however, because it is still fraught with technical difficulties, including targeting the stem cells to demyelinated regions, controlling their proliferation, neutralizing myelin-inhibitory signals from the neurons, and finally inducing oligodendrocyte differentiation into myelin. Experts warn that although stem-cell transplants may promote remyelination, uncontrolled proliferation of stem cells can lead to tumors. Given the numerous unresolved technical hurdles to this technique, we do not expect such an approach to become available for the treatment of MS during our 2005-2020 study period. (For more information, see the following report: New options for treating neurological disease: stem-cell therapy. Decision Resources, Inc. *Spectrum, Therapy Markets and Emerging Technologies.* Issue 17, 2006.)

Neuroprotective Role of the Immune Response

Although the immune response has traditionally been considered detrimental, recent studies suggest that components of the immune attack may provide neuroprotection; therefore, completely preventing the immune response may be detrimental because doing so may not provide a permissive environment for remyelination. For instance, researchers have shown that the membrane attack complex of complement inhibits oligodendrocyte cell death by modifying the molecules that normally regulate the cell death process (Cudrici C, 2006; Soane L, 2001).

Evidence suggests that proteins beneficial to neurons are present in plaque regions, perhaps moderating the damage inflicted by the immune system on myelin. Indeed, brain-derived neurotrophic factor (BDNF), a protein that enhances neuronal survival, is expressed in the active inflammatory lesions of MS patients and may have some protective effects on neurons (Stadelmann C, 2002).

Although glatiramer acetate is touted for its immunomodulatory effects, emerging studies suggest that it may play a neuroprotective role as well. However, experts interviewed do not prescribe glatiramer acetate solely based on these findings; they prescribe the drug for its immunomodulatory role and consider these neuroprotective effects "nice to have." In EAE mice, glatiramer acetate increased levels of neurotrophic factors, including BDNF, in neurons and astrocytes to levels similar to those of healthy animals (Aharoni R, 2005). In addition, a comparative study in a rat model of EAE demonstrated that glatiramer acetate administration provided neuroprotection for retinal ganglion cells (RGCs) in optic neuritis (an early clinical manifestation of MS); Betaseron treatment did not exert a similar effect (Maier K, 2006). These data suggest that current disease-modifying therapies may provide more expansive protection from disease progression than previously thought. More-extensive research is needed to adequately assess current therapies' neuroprotective functions.

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Pharmacor

MULTIPLE SCLEROSIS 2005-2020

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Chapter 3

Epidemiology and Disease Populations

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.5401.2615 ♦ Fax +81.3.5401.2617

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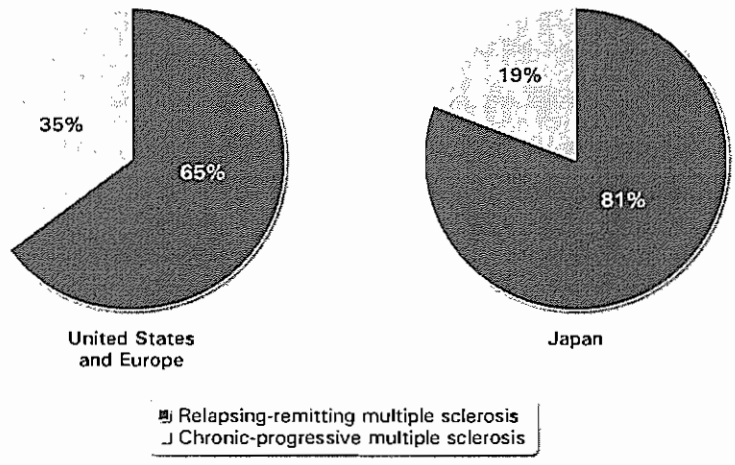
3. Epidemiology and Disease Populations

Key Findings

- The prevalence of diagnosed MS is growing as a result of improvements in diagnostic criteria and access to health care as well as increasing awareness of the disease.
- The age at diagnosis is declining because of reduced time between symptom onset and diagnosis of MS. Lower age at diagnosis combined with ever-increasing survival rates increases MS patients' length of therapy, thus representing long-term commercial opportunity.
- Surprisingly, epidemiological studies have shown that using the McDonald criteria does not increase the diagnosed prevalent population. Physicians interviewed do not expect revisions to the criteria to yield an increase.
- The low prevalence of MS in Japan and the requirement that Phase III trials be conducted in the Japanese population before a drug's launch diminish the commercial opportunity for MS drugs in this country. Few new agents will launch in Japan during our forecast period.

"Multiple sclerosis is now more frequently diagnosed with MRI diagnostic tests. This [increased prevalence] is probably not a real increase but mainly a result of more-frequent diagnosis by MRI exam."
—Neurologist, Italy

Dominance of Relapsing-Remitting Multiple Sclerosis Among Disease Subtypes



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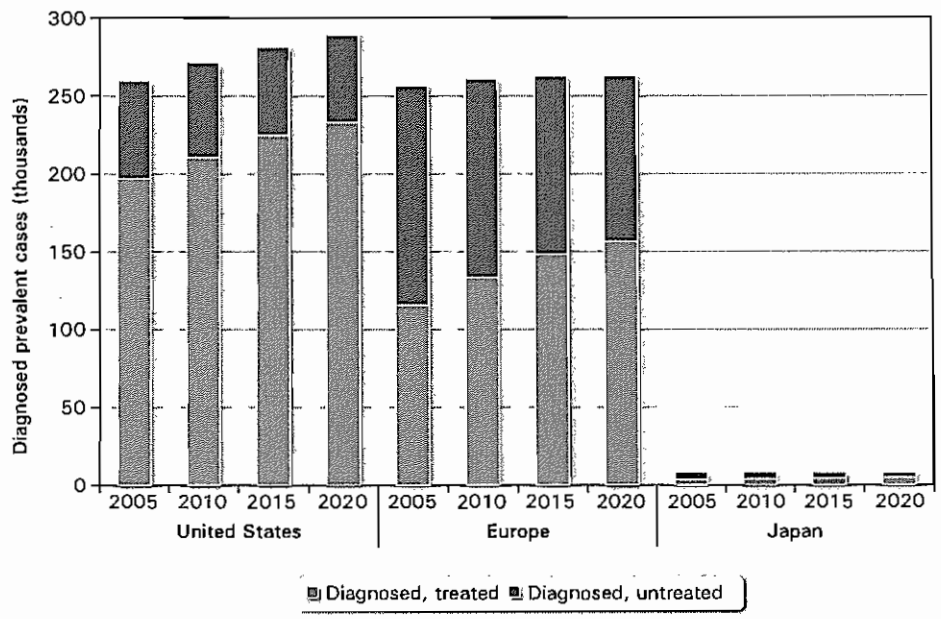
Treated and Untreated Diagnosed Multiple Sclerosis Patients by Region, 2005-2020



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Diagnosed Prevalent Cases of Multiple Sclerosis, 2005-2020

Region	2005	2010	2015	2020
United States	259,800	271,400	281,400	289,100
Europe	256,400	260,800	262,100	257,500
Japan	8,500	8,400	8,300	8,000
Total	524,700	540,600	551,800	554,600

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Source: Decision Resources, Inc.

Overview

Although the incidence of multiple sclerosis (MS) is relatively low in most areas of the world, the prevalence of MS can be high because of the disease's long clinical course (Zivadinov R, 2003). MS affects more than 500,000 people in the seven major pharmaceutical markets we cover (United States, France, Germany, Italy, Spain, United Kingdom, and Japan).

The onset of disease occurs most frequently between ages 20 and 35 in females and ages 35 and 45 in males (Thompson AJ, 1996). The mean age of the prevalent MS population is between 40 and 50 (Grant RM, 1998). In

most epidemiological studies, the prevalence of MS is one-and-one-half to two times higher in females than in males and more common in whites than in other races. Survival rates do not differ between the genders.

Disease Definition

Diagnosis of MS is made after long-term observation (usually a period of years) of symptoms and supporting diagnostic tests. MS is diagnosed by evidence of lesions in the central nervous system (CNS) that are disseminated in time and space (Poser CM, 2001); in other words, repeated episodes involve more than one area of the CNS (brain, spinal cord, and optic nerves). Clinical diagnosis of MS is based on historical information, neurological examination, and clinical evidence: magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF), evoked potentials, and blood tests to exclude confounding diagnoses (Lublin FD, 2002).

The length of time between clinical onset and a diagnosis of MS varies; current estimates indicate a lag of one to four years (Esbjerg S, 1999; Grimaldi LM, 2001; Sadovnick AD, 1993). However, studies conducted in European countries show that the lag between symptomatic onset and diagnosis has shortened continuously over the past 15 years (Nicoletti A, 2001; Pina MA, 1998; Pugliatti M, 2001). It is not entirely clear why this lag time has shortened, but some investigators believe it reflects a heightened awareness of MS, improved specialist care, and improved access to specialist care around the world (Dahl OP, 2004).

In most recent epidemiological studies, investigators use criteria developed by C.M. Poser and the Workshop on the Diagnosis of Multiple Sclerosis in the early 1980s to ascertain MS cases (Poser CM, 1983). The Poser criteria were developed specifically for research protocols and epidemiological studies, although some clinicians use the criteria for clinical purposes. The Poser criteria define two groups of cases (definite and probable), each with two subgroups (clinical and laboratory tested).

The International Panel on Multiple Sclerosis updated the diagnostic criteria for MS in 2001 (McDonald WI, 2001). These new diagnostic criteria (the McDonald criteria) formalize the use of MRI results in the overall diagnostic scheme, an adjustment that is enabling earlier diagnosis of MS. The new criteria allow diagnosis of "early-stage" MS to be made after a single relapse (i.e., a clinically isolated syndrome) (Fangerau T, 2004; Lublin FD, 2002; Polman CH, 2005). The McDonald criteria also provide guidelines for the diagnosis of primary progressive MS (PP-MS) and recommend that the outcome of diagnostic evaluations be classified as "MS," "possible MS," or "not MS" (McDonald WI, 2001). Some researchers have criticized the McDonald criteria for their reliance on MRI in the diagnosis of MS, their potential to overestimate MS, and the reintroduction of the "possible MS" category (Giovannoni G, 2003; Poser CM, 2001). In a 2005 clarification of the McDonald criteria, the panel argued that these criteria are not nearly as dependent on MRI evidence as they are thought to be; indeed, it is possible to diagnose a case of MS with the McDonald criteria in the absence of MRI evidence (Polman CH, 2005).

Researchers in the United Kingdom suggest that the McDonald criteria allow individual interpretation within the diagnostic scheme, thereby permitting interobserver variability and ultimately limiting the criteria's usefulness (Fox CM, 2004). Other experts believe that the new criteria will lead to earlier diagnosis of MS but not necessarily to greater numbers of patients diagnosed with MS (Lublin FD, 2002).

A recent study that evaluated the differences in case ascertainment between the McDonald criteria and the Poser criteria suggests that the latter diagnostic approach results in identification of significantly fewer MS cases, at least in the early stages of the disease (Tintore M, 2003). In a 2005 investigation of 76 potential MS patients in Germany, Fangerau and colleagues found a slightly different result. Although McDonald-defined MS was diagnosed more often than clinically definite Poser-defined MS, when the clinical and laboratory-definitc cases were combined, there were more Poser-defined cases than McDonald-defined cases (Fangerau T, 2004).

In another epidemiological study that used both the Poser and McDonald criteria to estimate prevalence, researchers compared the prevalence rates obtained by the two sets of criteria and found that the Poser criteria detected one more case per 100,000 population than the McDonald criteria (Fox CM, 2004). In this study, conducted in Devon, England, the Poser criteria resulted in a prevalence of 118 cases of definite or probable disease per 100,000 people, compared with 117 cases of definite or possible disease per 100,000 people according to the McDonald criteria. In a similar study conducted in the Canary Islands, the difference in the number of cases diagnosed by each criteria was also very small; using Poser criteria, definite or probable MS was found in 77.5 per 100,000 people, and using McDonald criteria, definite or possible MS was found in 73.8 per 100,000 people (Aladro Y, 2005). These results defy the expectation that the McDonald criteria would identify a greater number of cases of MS, but additional studies are necessary to quantify the differences in case ascertainment between the two sets of criteria.

In this report, we provide prevalence estimates for MS cases that are diagnosed by physicians to be probable or definite, and we exclude possible MS cases. To enable international comparison, we used the diagnostic criteria of Poser and colleagues, which have been widely used in surveys performed since 1980 to classify MS cases in epidemiological studies (Poser CM, 1983).

Methodology Overview

We present the results of our epidemiology analysis in tables that detail the following: diagnosed prevalent cases and key sources used in our review. We present diagnosed prevalent cases of MS for males and females aged 10 or older because the disease is extremely rare in young children. Studies show that less than 1% of all MS cases have an onset earlier than age 10 (Boiko A, 2002). We sought population-based studies that reported both age- and gender-specific prevalence rates. We calculated diagnosed prevalent cases by multiplying age- and gender-specific prevalence figures by United Nations (U.N.) population projections for the 15-year forecast period (United

Table 3-1

Number of Diagnosed Prevalent Cases of Multiple Sclerosis and Drug-Treated Population in the Major Pharmaceutical Markets, 2005-2020

					Growth (%/year)		
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
United States	259,800	271,400	281,400	289,100	0.9	0.7	0.5
Relapsing-remitting MS	168,900	176,400	182,900	187,900	0.9	0.7	0.5
Drug-treated percentage	87%	88%	90%	90%			
Drug-treated population	146,900	155,200	164,600	169,100	1.1	1.2	0.5
Chronic-progressive MS	90,900	95,000	98,500	101,200	0.9	0.7	0.5
Drug-treated percentage	55%	58%	61%	63%			
Drug-treated population	50,000	55,100	60,100	63,800	2.0	1.8	1.2
Europe	256,400	260,800	262,100	257,500	0.3	0.1	(0.4)
Relapsing-remitting MS	166,700	169,500	170,400	167,300	0.3	0.1	(0.4)
Drug-treated percentage	56%	62%	67%	71%			
Drug-treated population	93,300	104,800	114,800	118,100	2.4	1.8	0.6
Chronic-progressive MS	89,700	91,300	91,700	90,200	0.4	0.1	(0.3)
Drug-treated percentage	25%	31%	36%	40%			
Drug-treated population	22,400	28,500	33,200	36,000	4.9	3.1	1.6
France	38,900	39,600	39,500	39,200	0.4	(0.1)	(0.2)
Relapsing-remitting MS	25,300	25,700	25,700	25,500	0.3	0.0	(0.2)
Drug-treated percentage	79%	81%	85%	87%			
Drug-treated population	20,000	20,800	21,800	22,200	0.8	0.9	0.4
Chronic-progressive MS	13,600	13,900	13,800	13,700	0.4	(0.1)	(0.1)
Drug-treated percentage	40%	42%	44%	46%			
Drug-treated population	5,500	5,800	6,100	6,300	1.1	1.0	0.6
Germany	84,300	84,600	84,700	82,200	0.1	0.0	(0.6)
Relapsing-remitting MS	54,800	55,000	55,100	53,400	0.1	0.0	(0.6)
Drug-treated percentage	64%	67%	72%	75%			
Drug-treated population	35,100	36,900	39,600	40,100	1.0	1.4	0.3
Chronic-progressive MS	29,500	29,600	29,600	28,800	0.1	0.0	(0.5)
Drug-treated percentage	29%	36%	42%	47%			
Drug-treated population	8,600	10,700	12,500	13,500	4.5	3.2	1.6
Italy	39,500	39,700	39,100	38,000	0.1	(0.3)	(0.6)
Relapsing-remitting MS	25,700	25,800	25,400	24,700	0.1	(0.3)	(0.6)
Drug-treated percentage	71%	73%	75%	77%			
Drug-treated population	18,300	18,800	19,100	19,100	0.5	0.3	0.0
Chronic-progressive MS	13,800	13,900	13,700	13,300	0.1	(0.3)	(0.6)
Drug-treated percentage	27%	34%	40%	45%			
Drug-treated population	3,700	4,700	5,500	6,000	4.9	3.2	1.8

(continued)

Table 3-1 (cont.)

Number of Diagnosed Prevalent Cases of Multiple Sclerosis and Drug-Treated Population in the Major Pharmaceutical Markets, 2005-2020

					Growth (%/year)		
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Spain	18,800	19,200	19,400	18,800	0.4	0.2	(0.6)
Relapsing-remitting MS	12,200	12,500	12,600	12,200	0.5	0.2	(0.6)
Drug-treated percentage	84%	85%	88%	89%			
Drug-treated population	10,200	10,600	11,100	10,900	0.8	0.9	(0.4)
Chronic-progressive MS	6,600	6,700	6,800	6,600	0.3	0.3	(0.6)
Drug-treated percentage	45%	48%	51%	53%			
Drug-treated population	3,000	3,200	3,500	3,500	1.3	1.8	0.0
United Kingdom	74,900	77,700	79,400	79,300	0.7	0.4	(0.0)
Relapsing-remitting MS	48,700	50,500	51,600	51,500	0.7	0.4	(0.0)
Drug-treated percentage	20%	35%	45%	50%			
Drug-treated population	9,700	17,700	23,200	25,800	12.8	5.6	2.1
Chronic-progressive MS	26,200	27,200	27,800	27,800	0.8	0.4	0.0
Drug-treated percentage	6%	15%	20%	24%			
Drug-treated population	1,600	4,100	5,600	6,700	20.7	6.4	3.7
Japan	8,500	8,400	8,300	8,000	(0.2)	(0.2)	(0.7)
Relapsing-remitting MS	6,900	6,800	6,700	6,500	(0.3)	(0.3)	(0.6)
Drug-treated percentage	44%	50%	57%	64%			
Drug-treated population	3,000	3,400	3,800	4,200	2.5	2.2	2.0
Chronic-progressive MS	1,600	1,600	1,600	1,500	0.0	0.0	(1.3)
Drug-treated percentage	25%	31%	40%	45%			
Drug-treated population	400	500	600	700	4.6	3.7	3.1
Major-market total	524,700	540,600	551,800	554,600	0.6	0.4	0.1
Relapsing-remitting MS	342,500	352,700	360,000	361,700	0.6	0.4	0.1
Drug-treated percentage	71%	75%	79%	81%			
Drug-treated population	243,200	263,400	283,200	291,400	1.6	1.5	0.6
Chronic-progressive MS	182,200	187,900	191,800	192,900	0.6	0.4	0.1
Drug-treated percentage	40%	45%	49%	52%			
Drug-treated population	72,800	84,100	93,900	100,500	2.9	2.2	1.4

Notes: Numbers reflect rounding. Estimates include people aged 10 years or older.

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Source: Decision Resources, Inc.

Table 3-2

Key Sources for Epidemiology Estimates—Multiple Sclerosis

Country	Source[a]	Source Study Disease Definition[b]
United States		
Diagnosed prevalence	Anderson DW, 1992; U.S. Department of Health and Human Services (NINCDS), 1985	Physician-diagnosed multiple sclerosis (MS)[c] (based on Poser criteria)
RR-MS and CP-MS	Benito-Leon J, 1998; Bufill E, 1995; Ford HL, 1998; Fukazawa T, 1992; Granieri E, 1996; Grimaldi LM, 2001; Hernandez MA, 2002; Kremenchutzky M, 1999; McDonnell GV, 1998; Nicoletti A, 2001	Poser criteria
France		
Diagnosed prevalence	Granieri E, 1996	Physician-diagnosed MS[c] (based on Poser criteria)
RR-MS and CP-MS	Benito-Leon J, 1998; Bufill E, 1995; Ford HL, 1998; Fukazawa T, 1992; Granieri E, 1996; Grimaldi LM, 2001; Hernandez MA, 2002; Kremenchutzky M, 1999; McDonnell GV, 1998; Nicoletti A, 2001	Poser criteria
Germany		
Diagnosed prevalence	Granieri E, 1996; Poser S, 1995	Physician-diagnosed MS[c] (based on Poser criteria)
RR-MS and CP-MS	Benito-Leon J, 1998; Bufill E, 1995; Ford HL, 1998; Fukazawa T, 1992; Granieri E, 1996; Grimaldi LM, 2001; Hernandez MA, 2002; Kremenchutzky M, 1999; McDonnell GV, 1998; Nicoletti A, 2001	Poser criteria
Italy		
Diagnosed prevalence	Granieri E, 1996	Physician-diagnosed MS[c] (based on Poser criteria)
RR-MS and CP-MS	Benito-Leon J, 1998; Bufill E, 1995; Ford HL, 1998; Fukazawa T, 1992; Granieri E, 1996; Grimaldi LM, 2001; Hernandez MA, 2002; Kremenchutzky M, 1999; McDonnell GV, 1998; Nicoletti A, 2001	Poser criteria
Spain		
Diagnosed prevalence	Benito-Leon J, 1998	Physician-diagnosed MS[c] (based on Poser criteria)
RR-MS and CP-MS	Benito-Leon J, 1998; Bufill E, 1995; Ford HL, 1998; Fukazawa T, 1992; Granieri E, 1996; Grimaldi LM, 2001; Hernandez MA, 2002; Kremenchutzky M, 1999; McDonnell GV, 1998; Nicoletti A, 2001	Poser criteria
United Kingdom		
Diagnosed prevalence	Robertson N, 1996	Physician-diagnosed MS[c] (based on Poser criteria)
RR-MS and CP-MS	Benito-Leon J, 1998; Bufill E, 1995; Ford HL, 1998; Fukazawa T, 1992; Granieri E, 1996; Grimaldi LM, 2001; Hernandez MA, 2002; Kremenchutzky M, 1999; McDonnell GV, 1998; Nicoletti A, 2001	Poser criteria
Japan		
Diagnosed prevalence	Granieri E, 1996; Nanbyo Information Center, 2001	Physician-diagnosed MS[c] (based on Poser criteria)
RR-MS and CP-MS	Tanaka K, 2005	Poser criteria

a. Full source citations appear in "Bibliography." Parenthetical entries identify the survey upon which the source study is based and/or the date(s) of data collection.
b. See the text of the epidemiology section for details on how we used this information.
c. MS is a clinical diagnosis determined after long-term observation of symptoms and supporting diagnostic tests, including changes in cerebrospinal fluid, evoked responses, and imaging studies.

CP-MS = Chronic-progressive multiple sclerosis.
NINCDS = National Institute of Neurological and Communicative Disorders and Stroke.
RR-MS = Relapsing-remitting multiple sclerosis.

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Nations, 2005). We also present the diagnosed prevalent cases for each of the two MS subpopulations covered in this report (relapsing-remitting MS [RR-MS] and chronic progressive MS [CP-MS]; see the "Subpopulations" section later in this chapter for details on MS subpopulations).

Despite the large number of epidemiological investigations of MS conducted during the past 70 years in many parts of the world, defining the pattern of geographic distribution of MS is still a complicated task. Large differences in the incidence and prevalence of MS are observed from one region or country to another (Pugliatti M, 2002; Zivadinov R, 2003). These differences are partly explained by the heterogeneity of the epidemiological studies (discussed later in this chapter), but some studies also support the existence of genetic and environmental influences on the disease (Noseworthy JH, 2000). The relationship between MS prevalence and latitude—termed "the latitudinal gradient"—has been questioned. Some studies have found a higher prevalence of MS in northern latitudes than in southern latitudes (Zivadinov R, 2003). Other studies suggest that these observed differences may be attributed to differing susceptibilities in different ethnic populations rather than to the effects of climate and geography (Ebers GC, 2000; Pugliatti M, 2002; Sadovnick AD, 2002; Zivadinov R, 2003). A study of MS among U.S. veterans concluded that the latitudinal gradient is fading in the U.S. population. It was found to be much less pronounced among people who served in the military after 1964 than among people who served between 1941 and 1960 (Wallin MT, 2004).

A review of prevalence studies in the United Kingdom estimated that 78.2-99.6% of MS cases were ascertained (Forbes RB, 1999). If the prevalence estimates in these studies are adjusted for the unobserved cases, the difference in MS prevalence between Scotland and southern areas of the United Kingdom seems to be much less than suggested by prior surveys (Forbes RB, 1999). A meta-analysis evaluated 69 prevalence and 22 incidence studies to test whether the latitudinal gradient theory could be confirmed after adjustment to standard populations in regard to age and gender distribution (Zivadinov R, 2003). The study findings suggest that age and gender adjustment partially eliminate the apparent effect of latitude.

Variations in the world distribution of MS should be interpreted with caution. As stated previously, comparing MS prevalence studies poses a problem given the heterogeneity of the studies (Zivadinov R, 2003). The disease has been surveyed in different areas at different times using different diagnostic criteria; therefore, some observed differences may be spurious (Forbes RB, 1999). Although there are specific diagnostic criteria, making a definitive diagnosis of MS is frequently difficult, especially in cases with mild MS symptoms. Published epidemiological studies of MS use a wide range of case-finding methods, from surveys of patients and review of general practitioner records to full workups by neurological specialists. Not surprisingly, these various methodologies result in considerable variation in prevalence estimates.

Other methodological differences that affect comparability of MS studies include case ascertainment procedures, denominator characteristics (size, age, gender, and ethnicity of population surveyed), quantification of

numerators, and definitions of incidence and prevalence (Poser CM, 1994; Zivadinov R, 2003). Complete case ascertainment depends on a variety of factors that are known to vary from one geographic area or country to another. The availability of trained neurologists, access to medical care, local medical expertise, availability of new diagnostic procedures, and public awareness of MS all play a crucial role in complete case ascertainment (Rosati G, 2001; Sloka JS, 2005).

To estimate the burden of MS, we sought studies that were based in the general population (country-specific, when available) and included people who have been formally diagnosed with a definite or probable case of MS. In studies that included possible cases in their prevalence figures, we assumed (based on several studies) that 14% of MS cases were classified as possible cases and excluded that proportion of patients from the prevalence estimates (Bufill E, 1995; Ford HL, 2002; Rice-Oxley M, 1995; Robertson N, 1996). There are few large population-based registries for MS (Ford HL, 2002; Robertson N, 1996); out of necessity, we relied on regional studies to obtain country-specific prevalence estimates.

Major-Market Profiles

United States

In 1975, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) initiated a series of nationwide surveys to determine the extent and impact of certain neurological disorders in the United States (United States Department of Health and Human Services, 1985). The NINCDS estimated diagnosed MS prevalence by surveying physician-diagnosed MS through a probability sample of physicians and short-term general hospitals in the 48 contiguous states (United States Department of Health and Human Services, 1985). The NINCDS survey included possible, probable, and definite cases of MS. It estimated that on January 1, 1976, there were 123,000 MS patients reported in the United States (a prevalence of 58 cases per 100,000 people per year).

Although the methodology of the NINCDS survey was rigorous, application of its reported prevalence to the 1990 U.S. population would likely underestimate the number of prevalent cases of MS in the United States. Increased survival, for instance, would tend to cause estimates of prevalence to be higher than estimates from past decades (Wynn DR, 1990). For example, among residents of Olmsted County, Minnesota, MS prevalence per 100,000 people per year was 171 in 1985 (adjusted to the 1950 U.S. white population), an increase of 50% over the prevalence of 113 in 1978 (Anderson DW, 1992). After investigating possible reasons for the increase, the researchers of the Olmsted County study concluded that the disparity was chiefly attributable to methodological variation and only partly explained by trends in survival. D.W. Anderson and colleagues, the authors of an article that revised the NINCDS prevalence estimates, suggested that the national survey prevalence should be increased by 50% because of the finding in Olmsted County (Anderson DW, 1992). The authors adjusted the 1976 NINCDS estimates to reflect the U.S. population in 1990, increased MS prevalence by 50%, and further increased the prevalence to account for

cases that might have been missed for methodological reasons (Anderson DW, 1992). The revised estimates of Anderson and colleagues indicate that 250,000-350,000 people in the United States in 1990 had physician-diagnosed, clinically definite, probable, or possible MS—a prevalence of 102-139 cases per 100,000 people per year.

In 2003, W.T. Mayr and colleagues published an analysis of data gathered in Olmsted County from 1985 to 2000, using a centralized diagnostic index at the Mayo Clinic and the Rochester Epidemiology Program Project, a shared database of all health care practitioners in the county (Mayr WT, 2003). They found that the crude prevalence of MS appeared to increase from 160 per 100,000 people in 1985 to 177 per 100,000 people in 2000, suggesting substantial growth in the MS population. However, when both rates were age- and gender-adjusted to the 1950 U.S. white population, prevalence was shown to decline—from 171 per 100,000 people in 1985 to 160 per 100,000 people in 2000. This finding suggests that the perceived increase in the crude prevalence may be due to shifts in the age distribution of the population rather than an actual increase in the true prevalence of MS. Adjusted to the 2000 white U.S. population, the overall prevalence was 191 per 100,000 people. Although the study represents the most recent large-scale, community-based epidemiological study of the prevalence of MS conducted in the United States, application of these estimates to the entire U.S. population could result in artificially inflated estimates. In fact, when we applied its age- and gender-specific prevalenees to U.N. population estimates for each year of our forecast period (United Nations, 2005), the prevalent population was nearly twice the size generally accepted by experts (Noseworthy JH, 2000; Pugliatti M, 2002; Rosati G, 2001).

To estimate the prevalence of MS in the insured population, G.C. Pope and colleagues conducted an epidemiological study using elaims data from a Midwestern fee-for-service insurance company, Medicare, and Medicaid (Pope GC, 2002). A diagnosis of MS was defined by the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9 CM) diagnosis code 340. Based on two years of claims data, the prevalence of MS was 240 per 100,000 people in the privately insured population, 360 per 100,000 people in the Medicare population, and 710 per 100,000 people in the Medicaid population. The relatively high prevalence estimates in the Medicare and Medicaid population reflect the faet that MS can disable working-age adults, who are then covered by public insurance programs. Because managed care is under-represented in the data set, the fee-for-service claims data are skewed to an insured population that is more likely to have MS. Numerous studies have documented that people who enroll in health maintenance organizations (HMOs) are healthier than people who remain in traditional fee-for-service insurance programs (Morgan RO, 1997; Riley G, 1996). For these reasons, the study results cannot be generalized to the U.S. population, and we chose not to use the study as a basis for prevalence estimates.

C.M. Poser, the principal author of the Poser criteria, has criticized the Anderson revision of the NINCDS prevalence estimates because the revision relies on changes in prevalence in only three counties in Colorado and Minnesota (Poser CM, 1992). In these counties, according to Poser,

genetically high-risk individuals of Scandinavian descent constitute a disproportionately large segment of the population. Poser argues that the revised prevalence estimates do not represent the U.S. population. This criticism can also be applied to the recent Olmsted County study. However, researchers continue to accept the prevalence estimates of the Anderson revision, and we chose to use this revision as the basis for our prevalence estimates (Noseworthy JH, 2000; Pugliatti M, 2002; Rosati G, 2001).

To estimate the number of diagnosed prevalent cases of MS, we have modified the 1976 prevalence from the NINCDS survey to reflect the aforementioned trends. First, we multiplied the age- and gender-specific NINCDS prevalence by U.N. population estimates in each year of our forecast (United Nations, 2005). Second, in light of the Olmsted County results for 1978, 1985, and 2000, we multiplied the prevalence by 1.5 to account for the probable undercounting of cases in the 1970s that resulted from less-precise diagnostic protocols (Anderson DW, 1992). Third, we multiplied the prevalence by 0.86 to remove the estimated 14% of cases classified as possible MS.

We estimate that the overall diagnosed prevalence of MS in the Unites States in people aged 10 or older in the first year of our study period was 101 cases per 100,000 people. Our diagnosed prevalence estimate of MS cases in the United States in the first year of our study period is higher than the estimate of 211,000 (+/- 20,000) cases suggested by data from patients' self-reports of MS diagnoses in the U.S. National Health Interview Survey (NHIS) (Noonan CW, 2002). The NHIS was conducted from 1982 to 1996 in a sample of the noninstitutionalized U.S. population (Noonan CW, 2002). The accuracy of diagnoses of the NHIS is limited because the study relies on self-reported information; therefore, we decided not to use it as a basis for prevalence estimates of MS.

France

Data on the prevalence of MS in France are limited. In addition, no estimates of the prevalence of MS in France have been published in the past within the last 20 years. From the late 1970s to the early 1980s, prevalence estimates in France ranged from 28 to 58 cases per 100,000 people per year, indicating MS prevalence that is similar to prevalence in Spain and mainland Italy (Pugliatti M, 2002; Rosati G, 2001). In a population-based study in Hautes-Pyrenees, the diagnosed prevalence of probable and definite MS was estimated at 40 cases per 100,000 people per year in 1983 (Berr C, 1989). In 1986, the Institut National de la Santé et de la Recherche Médicale (INSERM) estimated the prevalence of MS to be at least 50 cases per 100,000 people per year (Kurtzke JF, 1996). It is possible that these prevalences, which were estimated 20-25 years ago, are underestimates; improvements in case-finding procedures and classification of cases according to generally accepted diagnostic criteria have emerged since then.

Because no age- and gender-specific MS prevalence estimates are available for France, we assumed the prevalence of MS to be similar in France and Italy; therefore, we applied the prevalence found in a Ferrara, Italy, study to the French population (Granieri E, 1996). The Ferrara study, conducted in a

large community of approximately 360,000 people, estimated that the overall prevalence of Poser-defined definite or probable MS was 69.4 cases per 100,000 people per year in 1993 (Granieri E, 1996). This estimate is notably higher than the prevalence of 46.1 cases per 100,000 people per year found in the same region in 1981 (Granieri E, 1985). The authors of the Ferrara study note that the increased prevalence was most likely the result of increasing survival of MS patients because of improving supportive care and the ability of the researchers to trace additional patients who may have been missed in the previous surveys.

We multiplied age- and gender-specific prevalence from the Ferrara study (Granieri E, 1996) by corresponding U.N. population estimates for France to estimate the number of diagnosed MS cases (United Nations, 2005). We estimate that the overall diagnosed prevalence of MS in France in people aged 10 or older in the first year of our study period was 73 cases per 100,000 people.

Germany

Data on the frequency of MS in Germany are limited. Published studies in the early 1980s reported that prevalence of MS in Germany was 43-69 cases per 100,000 people per year (Rosati G, 2001). A decade later, prevalence of 85-127 cases per 100,000 people per year was reported in different areas of Germany (Poser S, 1995; Rosati G, 2001). The Hein report, which offers a review of multiple prevalence studies from several regions of Germany, estimates that MS prevalence in Germany is 149 cases per 100,000 people per year (Hein T, 2000). However, this estimate is probably high because many of the studies that Hein reviewed used definitions of MS that included possible cases. S. Poser (who, like most recent researchers, excludes possible cases of MS) estimates that prevalence in south Lower Saxony in 1994 was between 83 and 127 cases per 100,000 people (Poser S, 1995). According to G. Rosati, the prevalence figures from Germany suggest a rather even geographic distribution of MS and appear to be similar to figures reported from England and Wales, Iceland, Denmark, Sweden, and southern Norway during the same years (Rosati G, 2001).

The German Multiple Sclerosis Society (Deutsche Multiple Sklerose Gesellschaft, DMSG) has been developing a nationwide MS register since 2001; the aim of this register to conduct comprehensive surveillance of MS and thus quantify the burden of disease in Germany (Deutsche Multiple Sklerose Gesellschaft, 2005b). Currently, 15 clinics, hospitals, and research centers are involved in case ascertainment. Unfortunately, because no age- or gender-specific prevalence data have been made publicly available, we were unable to use the register for our estimates. The current DMSG prevalence estimate of MS in Germany is 120 cases per 100,000 people (Deutsche Multiple Sklerose Gesellschaft, 2005a).

None of the studies conducted in Germany reported age- or gender-specific estimates, which are required to forecast prevalence. Therefore, to estimate the number of diagnosed cases of MS in Germany, we used the age- and gender-specific prevalence from the Ferrara study (Granieri E, 1996). To adjust for the higher prevalence of MS in Germany relative to Italy, we

increased the age- and gender-specific Ferrara estimates by a factor of 1.5 and arrived at a prevalence of 104 diagnosed MS cases per 100,000 people per year, which is in the middle of the range of MS prevalence estimates for Germany.

Applying the age- and gender-specific prevalences of the Ferrara study to the U.N. population estimates for Germany and multiplying by 1.5, we estimate the overall prevalence of diagnosed MS in Germany to be 112 cases per 100,000 people in people aged 10 or older in the first year of our study period; our finding falls within the range estimated by S. Poser (Poser S, 1995) and is quite close to the current DMSG estimate. Also, as expected, our estimate is lower than the Hein report's estimate, which summarized prevalence estimates from many studies that reported possible, probable, and definite cases of MS (Hein T, 2000).

Italy

Prior to 1980, the prevalence of MS in Italy was considered low compared with prevalence in other European countries. The prevalence of MS in Italy may have been underestimated by most studies prior to 1980 because health care in Italy was not as well established as in other, more affluent countries in northern and central Europe (Rosati G, 1994). More-recent epidemiological surveys have yielded higher rates that indicate Italy may be a geographical high-risk area for MS (Pugliatti M, 2002). Higher prevalence estimates found in recent studies may result from improvement in diagnostic tools that enable an earlier and more efficient diagnosis assessment, as well as improvement in epidemiological methodology (Granieri E, 1995). During the past 20 years, the prevalence and incidence of MS in mainland Italy and its two major islands, Sicily and Sardinia, have been studied in detailed and repeated assessments. These studies find a range of 35 to 94 prevalent MS cases per 100,000 people per year in mainland Italy and Sicily (Granieri E, 1996; Nicoletti A, 2005b; Pugliatti M, 2002; Ragonese P, 2004; Rosati G, 2001; Solaro C, 2005).

The island of Sardinia may represent a remarkable exception to the relatively even distribution of MS in Italy. The most recent studies in large populations confirm a prevalence of 144 to 152 cases per 100,000 people per year in Sardinia, indicating that this Italian island has the highest prevalence of MS in Mediterranean Europe as well as one of the highest in the world (Granieri E, 2000; Pugliatti M, 2001). Sardinians are known to be an ethnically homogeneous community that differs from other Italian communities. The high prevalence of MS in Sardinia has been partly explained by the high frequency of a distinct genetic structure that increases susceptibility to MS and other autoimmune diseases (Granieri E, 2000).

We identified three additional recent population-based prevalence studies of MS in Italy that we did not use in this analysis for various reasons. First, a study published by C. Solaro and colleagues in 2005 estimated the prevalence of Poser-defined MS in the northwestern province of Genoa on December 31, 1997 (source population = 913,218) (Solaro C, 2005). The reported prevalence in this study was 94 cases per 100,000 people (67 per 100,000 for males, 118 per 100,000 for females). We did not use these data because the

results represent such a large difference from previously published estimates that we were reluctant to use them without further studies to substantiate such a sudden increase in prevalence. Also, the data were not sufficiently broken down by age to be used in our analysis. Second, a study published by A. Nicoletti and colleagues in 2005 estimated the prevalence of Poser-defined MS in Catania, Sicily, on December 31, 1999 (source population = 313,110) (Nicoletti A, 2005b). The reported prevalence in this study was 92 cases per 100,000 people (80.4 per 100,000 for males, 102.4 per 100,000 for females). We did not use this study for two reasons: 1) the prevalence estimates change drastically compared with past prevalence estimates and 2) the study was based in Sicily, which as an island of Italy is not the best source population from which to make countrywide estimates because of the probable genetic isolation of its population (much like Sardinia). Third, in 2004, P. Ragonese and colleagues estimated MS prevalence in Monreale, Sicily, on December 31, 2000 (source population = 29,493) (Ragonese P, 2004). The reported prevalence in this study was 71.2 cases per 100,000 people (48.5 per 100,000 for males, 93 per 100,000 for females). We did not use this study because it was based in Sicily and because of its small source population.

To estimate the diagnosed prevalence of MS in Italy, we used age- and gender-specific prevalence rates of MS from a large study conducted in the Ferrara province of Italy (Granieri E, 1996). The estimates of MS in Ferrara are in the upper range of prevalence estimates for mainland Italy and in the middle range of estimates for all of Italy. The study was the third investigation of MS frequency in Ferrara, and it is well established that repeated surveys in the same area improve case ascertainment. We multiplied the age- and gender-specific rates reported in the Ferrara study by the corresponding U.N. population estimates (United Nations, 2005). For the first year of our study period, we derived an estimate of 75 diagnosed, prevalent cases of MS per 100,000 people in Italy in people aged 10 or older.

Spain

As in Italy, the prevalence of MS in Spain was likely underestimated in the past. Prior to the late 1980s, MS prevalence studies in Spain were based on hospital records and mortality data, and Spain was considered an area of medium-low MS prevalence. In the early 1990s, several population-based prevalence studies of MS in defined geographical areas of relatively small populations (most fewer than 100,000) were conducted using a broad methodology, not simply relying on hospital case records (Benito-Leon J., 1998; Bufill E, 1995; Casquero P, 2001; Fernandez O, 1994; Hernandez MA, 2002; Modrego PJ, 1997). Recently published reports indicate a somewhat even distribution of MS prevalence in Spain and consistently show that Spain is an area of medium-high risk of MS (Pugliatti M, 2001; Pugliatti M, 2002). Age- and gender specific estimates of MS prevalence in Spain are available from recent studies, which report definite or probable MS prevalence ranging from 32 to 78 cases per 100,000 people per year (Aladro Y, 2005; Benito-Leon J., 1998; Bufill E, 1995; Casquero P, 2001; Fernandez O, 1994; Modrego PJ, 1997; Modrego PJ, 2003).

We based our prevalence estimates for Spain on a study conducted in Mostoles, a city in central Spain with a population of approximately 200,000

in 1996. The area is a closed health zone, depending exclusively on a single neurology unit, and is part of a modernized national health system that provides free health services for all residents. The prevalence of Poser-defined definite or probable MS was reported as 43.4 cases per 100,000 people per year in 1998 (Benito-Leon J., 1998). All MS cases were confirmed by two independent neurologists. The prevalence in the Mostoles study falls near the middle of the range of reported prevalences in Spain. Because the study did not find any MS cases for males aged 65 or older, we extrapolated age-specific diagnosed prevalence data from the Italian study (Granieri E, 1996) for this gender and age-group. We multiplied the age- and gender-specific rates reported in the Mostoles study by the corresponding U.N. population estimates (United Nations, 2005). For the first year of our study period, we estimate a prevalence of 48 cases of MS per 100,000 people in Spain in people aged 10 or older.

United Kingdom

Epidemiological studies confirm a high prevalence of MS in the United Kingdom. In England and Wales, the prevalence reported from different areas over the past 15 years has varied from 74 to 131 cases per 100,000 people per year (Fox CM, 2004; Pugliatti M, 2002; Robertson N, 1995). The studies used a variety of methods for case ascertainment and different classification criteria. They were also spread over a number of years. Nonetheless, MS appears to be evenly distributed within England and Wales, with the majority of studies reporting prevalence rates in the low 100s per 100,000 people. The one study that found the prevalence of MS to be less than 80 cases per 100,000 people per year was conducted in Guernsey, which lies 100 miles south of mainland England at a latitude comparable to that of western France. Guernsey is unlikely to be representative of the population of the United Kingdom because it is a small island with a likely genetically isolated population (Sharpe G, 1995).

The prevalence of MS is considerably higher in Scotland than it is in England or Wales. Several studies in Scotland have provided data on prevalence ranging from 145 to 203 MS cases per 100,000 people per year (Murray S, 2004; Pugliatti M, 2002; Rothwell PM, 1998). More recently, a study in Tayside, Scotland, estimated the January 31, 2002, prevalence of Poser-defined probable and definite MS to be 236 cases per 100,000 people (Donnan PT, 2005). Prevalence rates in Scotland appear to be the highest detected in a large population anywhere in the world (Rosati G, 2001). The reason for the variation in prevalence between Scotland and the rest of the United Kingdom is not completely understood; however, genetic factors have been suggested. Populations with a high frequency of certain HLA-DR alleles (e.g., the *HLA-DR2* allele), such as the Scottish, often have the highest risk of MS (Noseworthy JH, 2000; Sadovnick AD, 2002). Additionally, there is no evidence of a latitudinal gradient within England or Wales, and the prevalence of MS increases sharply at the border of England and Scotland and then remains relatively constant within Scotland (Rothwell PM, 1998).

We based our diagnosed prevalent MS case estimates for the United Kingdom on a recent study in South Cambridgeshire, which had a population of approximately 290,700 people in 1991 (Robertson N, 1996). The study

used well-documented, thorough case-finding methods and reported on proportions of cases of definite and probable MS defined by standard clinical guidelines such as the Poser criteria (Poser CM, 1983). The prevalence of definite or probable disease was 131 cases per 100,000 people per year, which falls near the middle of the range of reported prevalence estimates for the United Kingdom (Robertson N, 1996). A recent serial prevalence study conducted in the Leeds Health Authority (estimated population of 728,840) reported a slightly lower prevalence of 93 cases per 100,000 people per year, which the authors explain may have resulted from the underascertainment of cases that commonly occurs when studying MS in large populations (Ford HL, 1998; Ford HL, 2002). The prevalence of MS estimated from the Leeds Health Authority study is on the low end of the range of prevalence estimates for the United Kingdom when Scotland estimates are included; therefore, we chose not to use it as a basis for our prevalence estimates.

Multiplying the age- and gender-specific prevalence estimates from the South Cambridgeshire study by U.N. population estimates for the United Kingdom, we estimate that in the first year of our study period, the prevalence of diagnosed MS in the United Kingdom was 142 per 100,000 people in people aged 10 or older (United Nations, 2005).

Japan

Prevalence surveys have shown MS to be uncommon in Japan, although this information relies on a large number of separate prevalence surveys that vary greatly according to case-classification definitions and completeness of case ascertainment (Martyn CN, 1997). Small studies conducted between 1975 and 1983 in ten Japanese cities extending from north to south reported that the prevalence of MS in Japan was 1 to 4 cases per 100,000 people per year (Rosati G, 2001). These studies were based on a small number of subjects and on the widely criticized 1972 Japanese criteria (Kuroiwa Y, 1975). Because MS prevalence in Japanese people living in Hawaii has been estimated at 9 cases per 100,000 people per year, methodological bias cannot be ruled out in these studies (Rosati G, 2001).

Between 1984 and 1994, according to the Ministry of Health, Labor, and Welfare (MHLW), the reported number of prevalent MS cases more than doubled in Japan, from 2,300 in 1984 to 4,637 in 1994, or close to 5 cases per 100,000 people per year (Ministry of Health LaW, 1996). According to the MHLW, a 35% increase occurred in the number of reported cases between 1990 and 1995. It is unlikely that this increase reflects a true change in prevalence; rather, it suggests a trend toward more complete identification and reporting of cases of MS, a trend also observed in Europe.

Another source of data on MS prevalence in Japan is the Nanbyo Information Center, a center for incurable diseases. Patients with such diseases register with the center to obtain medical care. According to the Nanbyo Information Center, 8,786 patients registered with MS in Japan in 2000 (Nanbyo Information Center, 2005b). However, the center's estimate of the number of MS cases in Japan in June 2002 was just 5,000 (Nanbyo Information Center, 2005a). The disparity between these estimates suggests that case ascertainment is inconsistent.

In the first rigorous prevalence study of MS conducted in Japan in almost 30 years, researchers concluded that the prevalence of MS is higher than previously believed: approximately 9 cases per 100,000 people (Houzen H, 2003). To identify cases of MS in the Tokachi province of northern Japan (estimated population of 361,726) in March 2001, researchers conducted a survey of 13 hospitals that treat neurological disorders in the province's single large city, Obihiro City. Only cases that were classified as definite MS according to the Poser criteria were included; both probable and possible cases were excluded. The authors of this study ascribe the high prevalence obtained to several possible factors, including a recent increase in the incidence of MS, improved case ascertainment, a greater number of neurological services in the Tokachi province, and a latitudinal gradient. Because this study did not present age-specific prevalence data, we chose to approximate the prevalence rate of MS in Japan based on a revision of the prevalence reported in the Ferrara, Italy, study (Granieri E, 1996).

We estimated the prevalence of MS in Japan to be one-tenth the prevalence reported in the Ferrara, Italy, study (Granieri E, 1996). We multiplied the Italian age- and gender-specific prevalences by 10% and applied these adjusted rates to the U.N. population estimates for Japan (United Nations, 2005). We estimate that the diagnosed prevalence of MS was 7 cases per 100,000 people in people aged 10 or older in the first year of our study period. Our estimate of diagnosed prevalent cases of MS in Japan correlates closely with the estimate of the recent study in Tokachi province and with the 2000 estimate released by the Nanbyo Information Center.

Subpopulations

The U.S. National Multiple Sclerosis Society has proposed four generally accepted clinical definitions that classify MS disease courses and subtypes: relapsing-remitting (RR), progressive-relapsing (PR), primary progressive (PP), and secondary progressive (SP) (Lublin FD, 1996). Only three subtypes—RR-MS, SP-MS, and PP-MS—are widely used internationally. Most experts agree that PR-MS is not sufficiently distinct from PP-MS; in medical practice, PR-MS patients are typically classified as PP-MS (Kremenchutzky M, 1999). Therefore, we do not provide prevalence estimates for MS according to these categories. Instead, we group all MS patients into two categories—RR-MS and chronic-progressive MS (CP-MS); the latter category includes both SP-MS and PP-MS—and provide prevalence estimates for each category. We base our grouping on the practices of interviewed experts, who segregate MS patients into two groups: patients whose disease is primarily inflammatory (RR-MS) and patients whose disease is primarily degenerative (CP-MS).

We estimate that RR-MS afflicts 65% of the diagnosed MS population and that 35% of the diagnosed MS population suffers from CP-MS. We multiplied the diagnosed prevalent cases of MS and total prevalent cases of MS by these proportions to provide country-specific estimates of total cases of RR-MS and CP-MS.

Our estimates are supported by the recent study on the prevalence of MS in Olmsted County, Minnesota, which found that 65% of definite MS cases

were RR-MS and 35% were CP-MS (Mayr WT, 2003; Pittock SJ, 2004). Furthermore, the expert opinion of C.M. Poser supports these estimates (Poser CM, 2001). These proportions also correlate with estimates provided in other epidemiological studies conducted in countries of interest that used the Poser criteria to identify MS cases and reported the distribution of MS subtypes in their findings (Aladro Y, 2005; Benito-Leon J., 1998; Bufill E, 1995; Ford HL, 1998; Fukazawa T, 1992; Granieri E, 1996; Grimaldi LM, 2001; Hernandez MA, 2002; Kremenchutzky M, 1999; McDonnell GV, 1998; Nicoletti A, 2001; Nicoletti A, 2005a; Nicoletti A, 2005b; Pina MA, 1998). In these studies, estimates range from 47% to 76% for RR-MS and 24% to 53% for CP-MS. It has been noted in the literature that most widely used criteria for diagnosing and defining MS were created using Western populations and thus might be inappropriately applied to other populations (Polman CH, 2005). With this in mind, we have used a study of disease course in metropolitan Tokyo to break down the Japanese MS cases; 81% of cases were RR-MS, and 19% were CP-MS (Tanaka K, 2005).

Diagnosis and Drug-Treatment Rates

Diagnosis rates will increase over the course of our study period as neurologists increasingly rely on MRIs to diagnose MS patients and, as a result, more patients are diagnosed at early stages of the disease. As one Spanish neurologist explains, "In the past, we had restrictions on MRI use, but today it's very, very easy to reach an MRI and we are giving an earlier diagnosis [of MS]. In comparison to the past years, the diagnosis is made very, very early." Experts interviewed point out that easier access to MRI has led to an increasing overdiagnosis of MS because some patients are misdiagnosed with the disease based on MRI findings. One expert states, "The first diagnosis of MS is critical and crucial, and I think that is where we have some problem. People have generally relied on MRI, but MRI is not as specific as some people might have thought, and there is a high rate of overdiagnosis when you rely only on MRI findings." Overdiagnosis may be the result of more patients being diagnosed earlier in the disease. A U.S. neurologist explains, "We may be overtreating some patients, because we can't predict their future clinical course." Experts admit that not all patients diagnosed with early-stage MS (also called clinically isolated syndrome [CIS]) will develop RR-MS; perhaps as many as 30% do not progress, but many experts prescribe disease-modifying therapies for early-stage MS patients.

We do not expect the emergence of biomarkers for MS to spur an increase in diagnosis rates because biomarker research in this indication is mainly focused on prognostic markers that would allow neurologists to predict the course of a patient's disease or on biomarkers that will determine whether a patient will respond to a therapy. One example of a genetic marker codeveloped with a therapy is BioMS Medical's MBP-8298, which appears effective in patients carrying the *HLA-DR2* or *HLA-DR4* genes; therefore, we expect that neurologists will determine a patient's genotype before initiating treatment with this drug. Experts interviewed are interested in the development of biomarkers as a diagnostic tool and stress that any biomarker developed for this purpose must clearly determine whether the disease is MS. As one expert points out, "In principle, you can talk about

pharmacogenomics being helpful. I don't know how far we can extrapolate it for MS because, yes, the *HLA-DR2* allele may be more common in patients with MS, but that's also a very common allele in the Caucasian population."

The growth in drug-treatment rates will be fueled by prescription of MS drugs (mostly disease-modifying agents) to patients in previously underserved subgroups, such as early-stage MS patients and CP-MS. Growing familiarity with and acceptance of disease-modifying therapies by neurologists and regulatory agencies will help to drive this increase in drug-treatment rates in the U.S. and European markets.

The net increase in drug-treatment rates will occur mostly in Europe because the European markets are not as penetrated as the U.S. market. Historically, regulatory agencies (specifically in the United Kingdom) have refused to reimburse patients for these costly drugs because they did not see a clinical benefit relative to drug cost. Now, regulatory agencies are relaxing their restrictions, and we expect drug-treatment rates to rise correspondingly. Drug-treatment rates will also increase in Japan during our forecast period, fueled by the availability of novel, more convenient therapies (i.e., Avonex in 2006).

Neurologists who specialize in MS and practice in centers that are accustomed and equipped to manage MS are familiar with the treatment benefits of disease-modifying drugs and are more likely to prescribe these agents to patients and to prescribe them sooner after diagnosis. General neurologists, on the other hand, especially those practicing at centers that do not specialize in MS therapy or are poorly equipped (i.e., do not have access to MRI), have traditionally been less likely to prescribe disease-modifying therapy. However, interviewed experts say this situation has been changing and will continue to change over the forecast period. As one expert notes, "Neurologists in general are becoming more and more aware of the situation [the complex symptoms of MS], and even community neurologists are paying a lot of attention to this possibility and they, in general, perform a very extensive diagnostic workup and try to identify the disease properly."

Untreated patients represent a significant patient population in the MS market: we estimate that of 524,700 diagnosed MS patients in the seven major markets under study, 165,000 are untreated (see Table 3-1). These patients are untreated because they have symptoms that are too mild to initiate treatment, do not respond to current therapies and have stopped taking disease-modifying agents ("quitters"), or refuse therapy. According to one Spanish neurologist, "Injection is always a problem for patients. Some patients stop interferons or stop drugs because they can no longer stay on the injections, not because of lack of efficacy. We have patients who stop the drugs for that, or patients not taking the drug as they should, because they don't want to inject themselves that much." One U.S. physician adds, "We are dealing with drugs that really change the person's outcome from the standpoint of their quality of life—basically, they have to inject themselves every day. They have to carry this little stuff when they go traveling on a trip. They have to put it on ice. They have to deal with the injection side effects. It's not trivial."

We forecast that only 10% of currently untreated patients will begin receiving treatment during our forecast period. This increase in the drug-treated population is the result of a greater number of disease-modifying therapies available on the market, particularly drugs with oral formulations, representing additional therapeutic options for patients. The monoclonal antibody (MAb) and altered peptide ligand (APL) scheduled to launch during our study period are not more-convenient than or as safe as currently available therapies. Oral therapies scheduled to launch during our forecast period have improved convenience, although the safety and efficacy of these drugs are not vastly superior to current therapies, with the exception of FTY-720, which has demonstrated better efficacy than current interferon beta (IFN-β) therapies and a modest safety profile. Despite their drawbacks, we anticipate use of emerging disease-modifying agents as third- or fourth-line therapies.

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MULTIPLE SCLEROSIS 2005-2020

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Chapter 4

Current Therapies and Treatment Trends

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.5401.2615 ♦ Fax +81.3.5401.2617

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4. Current Therapies and Treatment Trends

Key Findings

- Neurologists increasingly prescribe high-dose, high-frequency IFN-β therapies (Merck Serono/Pfizer's Rebif, Bayer Schering Pharma's Betaferon/Berlex's Betaseron) because of their perceived increased efficacy over low-dose, low-frequency therapies (Biogen Idec's Avonex). However, because of its low-frequency administration, Avonex is widely prescribed in early-stage MS.
- IFN-β therapies are used first-line in MS based on their efficacy and safety. These and other disease-modifying agents (glatiramer acetate [Teva Pharmaceuticals' Copaxone] and natalizumab [Biogen Idec/Elan's Tysabri]) are used primarily in RR-MS and SP-MS patients. If patients are refractory to these agents, chemotherapeutics and immunosuppressants are prescribed. Most PP-MS patients receive only symptomatic treatment.
- Glatiramer acetate is prescribed either first-line or second-line following IFN-βs and is increasingly used as first-line therapy because of its improved tolerability over the IFN-βs.
- Uptake of natalizumab since its 2006 relaunch in the United States and launch in Europe has been modest. Physician and patient concerns over fatal opportunistic infections associated with its use have relegated it to third-line therapy in patients refractory to IFN-βs or to glatiramer acetate and to patients with aggressive MS.

"The number of treatments will increase in the next five to ten years, but at the moment, interferon-beta is the first-line treatment and will be so for the next five to ten years."

—Neurologist, Spain

Comparison of Current Therapies for Multiple Sclerosis, 2007

Compound	Key Side Effects	Key Advantage	Key Disadvantage
Interferon-betas			
Interferon beta-1b	• Flulike symptoms	• Indicated for SP-MS	• Every-other-day injections
Interferon beta-1a (IM)	• Flulike symptoms	• Once-a-week dosing	• Intramuscular injection
Interferon beta-1a (SC)	• Flulike symptoms	• Better efficacy than less-frequent, lower-dose interferons (e.g., Avoex).	• Greater incidence of neutralizing antibodies than with other interferon-betas
Altered peptide ligands			
Glatiramer acetate	• Injection-site reactions	• No flulike symptoms	• Daily injection
Monoclonal antibodies			
Natalizumab	• Increased risk of opportunistic infections, including PML	• Very efficacious	• Risk of developing PML
Chemotherapeutics			
Mitoxantrone	• Increased risk of opportunistic infections, secondary AML, cardiotoxicity	• Indicated for SP-MS	• Lifetime dosing limit (requires monitoring)
Mycophenolate mofetil	• Increased risk of opportunistic infections	• Oral formulation	• Not indicated for MS

AML = Acute myelogenous leukemia; IM = Intramuscular; PML = Progressive multifocal leukoencephalopathy; SC = Subcutaneous; SP-MS = Secondary-progressive multiple sclerosis.

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Select Parameters for Current Therapies in Multiple Sclerosis, 2007

Parameters	Interferon Beta-1b	Interferon Beta-1a (IM)	Interferon Beta-1a (SC)	Glatiramer Acetate	Natalizumab	Mitoxantrone	Mycophenolate mofetil
Manufacturer	Bayer Schering Pharma[a] /Berlex	Biogen Idec	Merck Serono[b]/ Pfizer	Teva	Biogen Idec/ Elan	Serono/Amgen	Roche/ Aspreva
Brand name	Betaseron/ Betaferon	Avonex	Rebif	Copaxone	Tysabri	Novantrone	CellCept/ Munoloc
Dosage and delivery							
Dosage	250 mcg	30 mcg	22 mcg or 44 mcg	20 mg	300 mg	12 mg/m^2 (lifetime limit of 140 mg/m^2)	1 g
Route of administration	SC	IM	SC	SC	IV	IV	Oral
Frequency of administration	Once every other day	Once weekly	Three times weekly	Daily	Once monthly	Every 3 months	Twice daily
Line of therapy	First	First	First	Increasingly first	Second or third	Second or third	Third
Life-cycle parameters							
Launch date (US)	1993[c]	1996[e]	2002	1997	2004[g]	1987	1995[h]
Launch date (EU)	1996[d]	1997[f]	1999	2001	2006	1987	1998[h]
Launch date (JA)	2000	2006	N.A.	N.A.	2012	1987	1999[h]
Patent expiry (US)	2007	2013	2013	2014	2014	2005	2009
Patent expiry (EU)	2008	2005	2013	2015	2015	2005	2007[i]
Patent expiry (JA)	2008	2005	2013	2015	2015	2005	2012
Market parameters							
2005 sales[j]	$741.0	$1,359.2	$842.0	$1,006.9	$21.9[k]	$44.6	$4.9
2020 sales[j]	$490.3	$780.7	$1,226.0	$590.2	$630.8	$12.0	$3.2
2005 market share	18%	34%	21%	25%	1%	1%	<1%
2020 market share	9%	14%	22%	11%	11%	<1%	<1%

a. Schering is being acquired by Bayer and was renamed "Bayer Schering Pharma" in December 2006.
b. In January 2007, Merck KGaA completed the acquisition of Serono and renamed the company Merck Serono.
c. 2003 for secondary progressive multiple sclerosis (SP-MS) with relapses (US).
d. 1999 for SP-MS.
e. 2003 for early-stage MS.
f. 2002 for early-stage MS.
g. Withdrawn from the U.S. market in February 2005. Relaunched in July 2006 (US).
h. For transplant rejection. Not indicated for MS.
i. 2007 patent expiry date for Spain; 2010 for United Kingdom; 2011 for France, Germany, Italy.
j. In millions.
k. 2005 sales of natalizumab represent two months of sales before the drug was withdrawn from the market.

IM = Intramuscular; IV = Intravenous; N.A. = Not applicable; SC = Subcutaneous.

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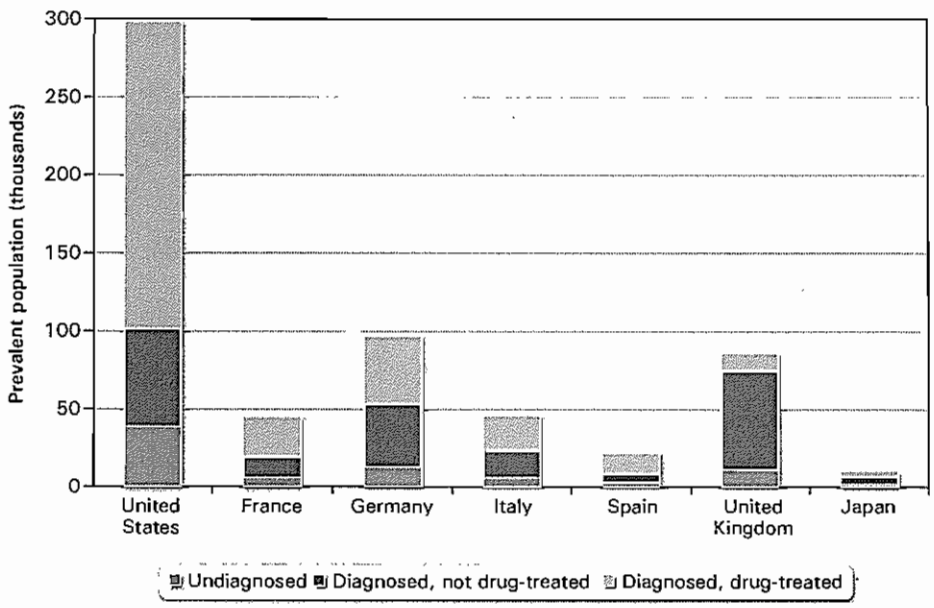
Diagnosis and Drug-Treatment Rates for Multiple Sclerosis in the Major Pharmaceutical Markets, All Populations, 2007



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Overview of Current Therapies

Because multiple sclerosis (MS) is an autoimmune disease, the mainstay of its treatment has been immunological pharmacotherapies that either are specific to the pathophysiology of MS (interferon beta [IFN-β] agents and the altered peptide ligand [APL] glatiramer acetate [Teva Pharmaceutical's Copaxone]) or more generally suppress the immune system (chemotherapeutic agents, immunosuppressants). The recent relaunch of the cell adhesion molecule inhibitor natalizumab has provided another immunomodifying treatment option, although it will not be as widely used as IFN-β agents or glatiramer acetate in MS treatment because of its potential for severe side effects. Table 4-1 compares the side effects, advantages, and disadvantages of current MS therapies.

IFN-βs, glatiramer acetate, and natalizumab are used primarily during the inflammatory stages of MS: relapsing-remitting MS (RR-MS) and secondary-progressive MS (SP-MS). SP-MS is considered inflammatory as opposed to degenerative only when the patient is still relapsing. These agents have all been shown to be "disease-modifying" (that is, they affect the underlying cause of the disease instead of mitigating symptoms of the disease such as fatigue), albeit with limited efficacy.

Table 4-1

Comparison of Current Therapies for Multiple Sclerosis, 2007

Compound	Side Effects	Advantages	Disadvantages
Interferon-betas			
	• Flulike symptoms • Injection-site pain • Injection-site reactions • Abnormal liver enzymes • Depression/suicidal ideation	• Modest efficacy • Good safety profile	• One-third of patients do not respond • Flulike side effects • Poor compliance because of dosing and formulation • Formation of neutralizing antibodies decreases efficacy • Efficacious only in relapsing MS
IFN-β-1b (Betaseron)	• Flulike symptoms • Injection-site pain • Depression/suicidal ideation • Injection-site reaction/necrosis • Abnormal liver enzymes • Cardiac arrhythmias • Reduction in lymphocytes and neutrophils	• Indicated for SP-MS • Subcutaneous injection • No refrigeration	• Every-other-day dosing schedule is onerous • Higher incidence of skin necrosis • Greater incidence of neutralizing antibodies • Must be reconstituted from powder
IFN-β-1a (IM, Avonex)	• Flulike symptoms • Depression/suicidal ideation • Decreased peripheral blood counts • Hypersensitivity reactions • Abnormal liver enzymes	• Once-weekly dosing • Fewer flulike side effects • Lower incidence of neutralizing antibodies • Prefilled syringes	• Intramuscular injection • Requires refrigeration
IFN-β-1a (SC, Rebif)	• Flulike symptoms • Injection-site pain • Injection-site reaction • Depression/suicidal ideation • Abnormal liver enzymes	• Subcutaneous injection • Better efficacy than less-frequent, lower-dose interferons (e.g., Avonex) • Easier dosing schedule to remember than Betaseron • Prefilled syringes	• Three-times-weekly injection • Greater incidence of neutralizing antibodies • Requires refrigeration

(continued)

Table 4-1 (cont.)

Comparison of Current Therapies for Multiple Sclerosis, 2007

Compound	Side Effects	Advantages	Disadvantages
Altered peptide ligands			
Glatiramer acetate (Copaxone)	• Injection-site reactions • Injection-site pain • Vasodilation	• Modest efficacy • No flulike symptoms • Subcutaneous injection • Prefilled syringes • Storage for up to 7 days at room temperature	• Daily injection
Monoclonal antibodies			
Natalizumab (Tysabri)	• Increased risk of opportunistic infections, including PML • Hypersensitivity reactions • Headache • Fatigue • Limb and joint pain	• Very efficacious • Once-monthly dosing	• Risk of developing PML • Usage requires registration in monitoring programs • IV administration
Chemotherapeutics			
	• Broad immunosuppressive properties • Increased risk of opportunistic infections • Hematologic toxicity • Nausea	• Greater efficacy in progressive forms of MS, aggressive RR-MS	• IV administration • Severe side-effect profile • Limited clinical trials in MS
Mitoxantrone (Novantrone)	• Cardiotoxicity • Increased risk of opportunistic infections, secondary AML	• Indicated for SP-MS • Effective in SP-MS, some forms of aggressive RR-MS	• IV administration • Lifetime dosing limit • Severe side-effect profile
Mycophenolate mofetil (CellCept)	• Increased risk of opportunistic infections • Diarrhea • Decreased white blood cell count • Sepsis • Vomiting	• Oral formulation • Efficacious	• Daily dosing • Not indicated for MS

AML = Acute myelogenous leukemia; IM = Intramuscular; IV = Intravenous; MS = Multiple sclerosis; PML = Progressive multifocal leukoencephalopathy; RR-MS = Relapsing-remitting multiple sclerosis; SC = Subcutaneous; SP-MS = Secondary progressive multiple sclerosis.

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The modest efficacy and good safety profile of IFN-βs and glatiramer acetate have allowed these agents to attain the status of first-line therapy for MS, while natalizumab has been relegated to a second- or third-linc therapy. All of these agents can, to varying degrees, alter the natural progression of MS by reducing relapse rates, easing lesion load (as measured by magnetic resonance imaging [MRI]), and slowing sustained disability progression in the short term (as measured by the Kurtzke Expanded Disability Status Scale [EDSS]).

The more general and broader immunosuppressive therapies (e.g., chemotherapeutics) are prescribed during the degenerative stages of MS (SP-MS and occasionally in primary-progressive [PP-MS], together known as chronic-progressive MS [CP-MS]), in which the aforementioned disease-modifying drugs are not effective. However, the immunosuppressive drugs are plagued by severe side effects, so they are used as a last resort and have small patient shares.

Table 4-2 provides Decision Resources' estimates of patent and exclusivity expiries of key products. Note that this report does not cover drugs that

Table 4-2

Key Patent and Exclusivity Expiries of Drugs Used to Treat Multiple Sclerosis, 2007

Drug	United States	France	Germany	Italy	Spain	United Kingdom	Japan
IFN-β-1b	2007[a]	2008[a]	2008[a]	2008[a]	2008[a]	2008[a]	2008[a]
IFN-β-1a (IM)	2013[a]	2005[a]	2005[a]	2005[a]	2005[a]	2005[a]	2005[a]
IFN-β-1a (SC)	2013[a]	2013[a]	2013[a]	2013[a]	2013[a]	2013[a]	2013[a]
Glatiramer acetate	2014[a]	2015[a]	2015[a]	2015[a]	2015[a]	2015[a]	2015[a]
Natalizumab	2014[a]	2015[a]	2015[a]	2015[a]	2015[a]	2015[a]	2015[a]
Mitoxantrone	2005[a]	2005[a]	2005[a]	2005[a]	2005[a]	2005[a]	2005[a]
Mycophenolate mofetil	2009[a]	2011[a]	2011[a]	2011[a]	2007[a]	2010[a]	2012[a]
Methotrexate	EXP	EXP	EXP	EXP	EXP	EXP	EXP
Cyclo-phospha-mide	EXP	EXP	EXP	EXP	EXP	EXP	EXP
Azathioprine	EXP	EXP	EXP	EXP	EXP	EXP	EXP
Methyl-prednisolone	EXP	EXP	EXP	EXP	EXP	EXP	EXP

Explanation of Footnotes:

In determining expiry dates we identify the lapse of the latest significant form of market exclusivity as indicated by the footnote letter.

a. Expiry of key patent (includes any relevant extensions, e.g., Hatch-Waxman, SPC, or Japanese patent extension)

Note: Our patent and exclusivity expiration dates are based on the latest information from the following sources: FDA Orange Book, IMS Patent Focus, and a review of ongoing news and litigation found in a variety of proprietary sources.

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address only symptoms of MS, such as fatigue or spasticity; we focus exclusively on disease-modifying therapies.

Recombinant Interferons

Overview

Three groups of IFNs have been identified—alpha (α), beta (β), and gamma (γ). These IFNs differ in their cell of origin, reaction with antibodies, and chemical properties. The IFN-βs are considered first-line therapy in the treatment of RR-MS because they have shown an immunomodulatory effect in clinical trials in MS (Jacobs LD, 1996; PRISMS Study Group, 1998; PRISMS Study Group, 2001; The IFNB Multiple Sclerosis Study Group, 1993; The IFNB Multiple Sclerosis Study Group, 1995). Three drugs for MS have been developed from recombinant versions of IFN-β: IFN-β-1a (Biogen Idec's Avonex and Merck Serono [formerly Serono]/Pfizer's Rebif) and IFN-β-1b (Bayer Schering Pharma [formerly Schering]'s Betaferon/Berlex's Betaseron).

The three drugs have a similar side-effect profile; flulike symptoms are of greatest concern among physicians interviewed. Because these symptoms appear after each injection, those drugs with less-frequent dosing have a lower incidence of side effects (see Table 4-1).

None of the commercially available IFN-β drugs are completely efficacious in controlling the progression of MS; in terms of the relative efficacy of the three available IFN-β therapies for the treatment of MS, evidence from clinical trials suggests a dose-response curve (EVIDENCE Study Group, 2001; Panitch H, 2002). IFN-β therapies that are administered at higher doses and/or more frequently (IFN-β-1b and Rebif) appear to be more effective in reducing relapse rates and lesion loads than therapies administered at lower doses and less frequently (i.e., Avonex) (Deisenhammer F, 2000; Goodin DS, 2002).

Mechanism of Action

The precise mechanism of action of IFN-β agents is unclear; however, these drugs have effects at several levels of the inflammatory cascade. IFN-βs reduce T-cell migration across the blood-brain barrier (BBB), suppress T-cell proliferation, and alter the T-cell cytokine secretion repertoire from relatively proinflammatory T_H1 to relatively anti-inflammatory T_H2 response (Yong VW, 1998).

Formulation

Recombinant IFN-βs are available only in injectable formulations. All three marketed IFN-βs come in prefilled syringes or a reconstitutable lyophilized tablet. IFN-β-1a, both in subcutaneous (SC, Rebif) and intramuscular (IM, Avonex) formulations, requires refrigeration. Betaseron is now available as a refrigeration-free lyophilized powder formulation, making it easier for patients to store, and a prefilled syringe containing the diluent is available in all major markets. In July 2006, a Betaseron autoinjector was launched in the United States.

Interferon Beta-1b

Betaseron, a recombinant form of IFN-β, was the first therapy approved for RR-MS (see Table 4-3). The drug was initially launched in the United States in 1993 for RR-MS (see Table 4-4 for more information on Betaseron in RR-MS clinical trials), where it received orphan-drug status. In 2003, the agent received additional approval for SP-MS (with relapses) in the United States (see Table 4-5 for more information on Betaseron in SP-MS clinical trials). Betaseron is available in Europe for use in RR-MS patients, SP-MS patients with relapses, and SP-MS patients without relapses. In Japan, Betaseron was the only approved IFN-β agent for RR-MS therapy until November 2006, when Avonex was launched in this market. A higher-dose formulation of

Table 4-3

Key Facts: Betaseron
Interferon Beta-1b
Launch Date: 1993 (US), 1996 (EU), 2000 (JA) for RR-MS; 2003 (US) for SP-MS with relapses; 1999 (EU) for SP-MS; 2006 (US, EU) for early-stage MS.
Brand Name and Marketer: Bayer Schering Pharma's Betaferon/Berlex's Betaseron.
Decision Resources' Expected Generic Entry: 2012 (US); 2008 (FR, GE, IT, SP, UK), post-2020 (JA).
Formulation and Dose: 250 mcg SC injection once every other day.
Mechanism of Action: The precise mechanism of action is unclear. However, IFN-β reduces T-cell migration across the BBB, suppresses T-cell proliferation, and alters the T-cell cytokine secretion repertoire in favor of anti-inflammatory cytokine response. Avonex and Rebif have similar mechanisms of action.
Side Effects: Flulike symptoms; injection-site pain; injection-site reaction/necrosis; depression/suicidal ideation; abnormal liver enzymes, cardiac arrhythmias, reduced number of lymphocytes; transient reduction in neutrophil levels; development of NAbs that can decrease drug efficacy.
Development Activity: Betaseron has received approval for treatment of early-stage MS (or clinically isolated syndrome [CIS]) from both the FDA and the EMEA. Results of the Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial in the early-stage MS patient population demonstrate that Betaferon reduced the development of RR-MS by 50% compared with placebo. Bayer Schering and Berlex are conducting another trial, the Betaferon in Early Relapsing Remitting Multiple Sclerosis Surveillance Trial (BEST), that is assessing long-term effects of Betaseron in early-stage RR-MS. The companies are conducting the Interferon Beta-1a Versus Interferon Beta-1b Observation of Efficacy (ABOVE) trial to compare efficacy of Betaseron with that of Avonex. The Betaferon Efficacy Yielding Outcomes of a New Dose (BEYOND) study is comparing the efficacy of two different doses of Betaseron (the approved 250 mcg SC dose and a 500 mcg SC dose) to glatiramer acetate. Bayer Schering and Berlex are comparing the safety and tolerability of Betaseron with Rebif regarding injection-site reactions.
Differentiating Features: Betaseron's approval for SP-MS will allow the drug to hold its market share. Long-term follow-up studies demonstrate the continued efficacy and safety of Betaseron in RR-MS patients over 12 years. The study is slated to last 16 years and is the longest follow-up study for RR-MS treatment. Results of the Independent Study of Interferon (INCOMIN) trial demonstrated that Betaseron had superior efficacy to Avonex in RR-MS (Durelli L 2002). Betaseron has an inconvenient dosing schedule (injection every other day) that may hinder its widespread use in a patient population that may not have very active disease and whose treatment decision would be more swayed by convenience than efficacy.
BBB = Blood-brain barrier; EMEA = European Medicines Agency; IFN = Interferon; NAbs = Neutralizing antibodies; RR-MS = Relapsing-remitting multiple sclerosis; SC = Subcutaneous; SP-MS = Secondary progressive multiple sclerosis.
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Source: Decision Resources, Inc.

Table 4-4

Comparative Efficacy of Multiple Sclerosis Therapies in Phase III Trials for RR-MS, 2007

End Point	Betaseron	Avonex	Rebif	Glatiramer acetate	Natalizumab	Mitoxantrone
Relapse rate reduction at two years vs. placebo	13% or 31% (depending on the dose)[a]	18% (Jacobs L, 1996)[b]	29% or 32% (depending on the dose; PRISMS Study Group, 1998)	29% (however, data are not significant: p=0.055; Johnson K, 1995)	68% (Polman CH, 2006)	68% (Hartung HP, 2002)
Median time (days) to first relapse at two years (Galetta S, 2002)	295	331	228 and 288	287	N.A.	No relapses occurred in two years
Reduction in disease progression (Galetta S, 2002)	29%	37%	23% and 31%	12%	42%	7% of patients progressed vs. 19% with placebo
Lesion volume MRI activity at two years (BOD as measured with proton density T2-weighted MRI)	No increase in treated patients vs. 20% increase in lesion area for placebo (IFNβ MS Study Group, 1995; Paty D, 1993)	No difference from placebo (small number of scans).	Decrease of 1.2% for 22 mcg and 3.8% for the 44 mcg dose vs. an increase of 10.9% for placebo	No change (however, small number of patients in the study, n=27)	Decrease of 83% for 300 mg dose, vs. placebo	Increase of 0.29 vs. increase of 1.94 in placebo group
Number of new active lesions (Gd-enhanced MRI activity)	N.A., but 80% reduction in new, recurrent, or enlarging lesions relative to control (Ge Y, 2000)	52% reduction vs. placebo (0.8 mean number of lesions at two years in all treated patients vs. 1.65 for placebo)	Reduction in number of active lesions of 67% and 78% for 22 mcg and 44 mcg, respectively, vs. placebo	Reduction of 0.2 lesions per year from baseline vs. an increase of 0.5 lesions from baseline for placebo (p=0.03, but only for T1-weighted lesions, not T2-weighted lesions)	92% reduction relative to control	None vs. 16% with placebo
Increase in injection-site reactions, relative to placebo	85% vs. 37% for placebo	4% vs. 1% for placebo	39% and 40% (for 22 mcg and 44 mcg, respectively) vs. 22% for placebo	49% vs. 11% for placebo	None reported	N.A.
NAbs at two years	36% (175 mcg dose)	14% (132 mcg dose	24% for 22 mcg and 12.5% for 44 mcg	None	6% (persistent binding antibodies) at 6 months[c]	N.A.

(continued)

Table 4-4 (cont.)

Comparative Efficacy of Multiple Sclerosis Therapies in Phase III Trials for RR-MS, 2007

End Point	Betaseron	Avonex	Rebif	Glatiramer acetate	Natalizumab	Mitoxantrone
Frequency of administration/ route	Every other day/SC	Weekly/IM	Three times weekly/SC	Daily/SC	Monthly/IV	Every 3 months/IV[d]

a. Data are for low (50 mcg every other day) or high (250 mcg every other day) doses.
b. Full source citations appear in "Bibliography." Parenthetical entries identify the study from which these data were taken.
c. Binding antibodies are antibodies generated against the drug and are not necessarily NAbs (antibodies against the drug that reduce its efficacy). The difficulty in designing laboratory assays to test NAb levels of natalizumab will likely make these numbers hard to determine.
d. Data reported here using a dose of 12 mg/m^2. A lower dose, 5 mg/m^2, was also examined in this study. Results for the lower dose were intermediate, between the high dose and placebo, and are not detailed here.

BOD = Burden of disease; Gd = Gadolinium; IM = Intramuscular; IV = Intravenous; MRI = Magnetic resonance imaging; N.A. = Not applicable; NAbs = Neutralizing antibodies; RR-MS = Relapsing-remitting multiple sclerosis; SC = Subcutaneous.

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Betaseron (500 mcg) is being investigated in a Phase III trial for improved efficacy compared with both the current dose of Betaseron (250 mcg) and glatiramer acetate in RR-MS.

In 2006, Betaseron received additional approval for use in early-stage MS in the United States and Europe, making it the first and only high-dose, high-frequency IFN-β therapy indicated for this MS patient population. To be diagnosed with early-stage MS, patients must have experienced a first clinical episode suggestive of RR-MS and have MRI data consistent with RR-MS. These approvals are based on findings from the Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study (see Table 4-6 for more information on Betaseron in early-stage MS clinical trials).

The BENEFIT study was a multicenter, randomized, placebo-controlled trial that examined the safety and efficacy of 250 mcg Betaseron administered subcutaneously every other day for two years. The primary end points were progression to clinically definite MS (CDMS) based on clinical criteria (a second demyelinating event or an EDSS progression of 1.5 or more points) and the time to developing CDMS according to the McDonald criteria, a set of diagnostic criteria that formalize the use of MRI in the overall MS diagnosis (McDonald WI, 2001). The secondary end point was the formation of new brain lesions as detected by MRI.

Two-year results from the BENEFIT study demonstrate the efficacy of Betaseron in prolonging conversion to CDMS (Kappos L, 2006b). Based on the clinical criteria, early-stage MS patients who began Betaseron therapy after a first demyelinating event demonstrated a 50% reduction in the risk of developing RR-MS compared with placebo. At two years, Betaseron

Table 4-5

Comparative Efficacy of Multiple Sclerosis Therapies in Phase III Trials for SP-MS, 2007

End Point	Betaseron	Avonex	Rebif
Relapse rate reduction at two years vs. placebo[a]	30% (European Study Group, 1998; Kappos L, 2001)[b]	33% (Cohen JA, 2002)	47% for 22 mcg dose; 38% for 44 mcg dose among patients with relapses (Li DK, 2001; SPECTRIMS Study Group, 2001)
Median time (days) to first relapse at two years (Galetta S, 2002)	644	N.A.	476 for 22 mcg; 494 for 44 mcg
Reduction in time of EDSS worsening	32.1%	No difference from placebo	No difference from placebo
Reduction in disease progression (Galetta S, 2002)	21.7%	No difference from placebo	No difference from placebo
Reduction in MS Functional Composite (MSFC) worsening	N.A.	40.4%	N.A.
Lesion volume MRI activity at two years (BOD as measured with proton density T2-weighted MRI)	5% decrease vs. 8% increase with placebo	45.6% reduction vs. placebo	Decrease of 0.5% for 22 mcg and 1.3% for 44 mcg vs. 10% increase with placebo
Number of new active lesions (Gd-enhanced MRI activity)	N.A.	69.1% reduction in volume vs. placebo	78% reduction for 22 mcg, 89% reduction for 44 mcg in *combined* T1-Gd and T2 analyses
Increase in injection-site reactions, relative to placebo	43.6% vs. 10.3% for placebo	5%	1 in 9,600 injections for 22 mcg; 1 in 3,800 injections for 44 mcg
Reduction in MS-associated steroid use	53.6% vs. 67.9% for placebo	29.6%	59% for 22 mcg; 66% for 44 mcg
NAbs at two years	27.8%	3.3% (NAb titer >= 20 U/mL)	20.6% for 22 mcg; 14.7% for 44 mcg
Frequency of administration/route	Every other day/SC	Weekly/IM	Three times weekly/SC

a. Note that other trials have been run on chronic-progressive MS (CP-MS) populations without distinguishing between secondary progressive MS (SP-MS) and primary progressive MS (PP-MS) patients. For example, a Phase II trial of glatiramer acetate in CP-MS patients included both SP-MS and PP-MS patients (PROMISE trial); see Table 4-7 for details of this trial. In addition, the AFFIRM trial demonstrated efficacy of natalizumab in relapsing forms of MS with no distinction made between patients with relapsing-remitting MS (RR-MS) or with SP-MS with relapses. See Table 4-4 for details on the AFFIRM trial.

b. Full source citations appear in "Bibliography." Parenthetical entries identify the study from which these data were taken.

BOD = Burden of disease; EDSS = Expanded Disability Status Scale; Gd = Gadolinium; IM = Intramuscular; MRI = Magnetic resonance imaging; N.A. = Not applicable; NAbs = Neutralizing antibodies; SC = Subcutaneous; SP-MS = Secondary progressive multiple sclerosis.

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Table 4-6

Comparative Efficacy of Multiple Sclerosis Therapies in Clinical Trials for Early-Stage MS, 2007

End Point	Betaseron	Avonex	Rebif
Relapse rate reduction at two years vs. placebo	N.A. (Kappos L, 2006)[a]	44% (Beck RW, 2002)	23% (rate of 0.33 vs. 0.43 with placebo; Comi G, 2001)
Median time (days) to second relapse at two years	618 vs. 225 with placebo in 25% of patients who converted	N.A.	569 vs. 252 with placebo in 30% of patients who converted
Reduction in conversion to clinically definite MS at two years	50%	49%	61%
Reduction in disease progression (Galetta S, 2002)	16%	47%	No difference vs. placebo
Lesion volume MRI activity at two years (BOD as measured with proton density T2-weighted MRI)	Mean decrease of 888 mm^3 vs. 432 mm^3 decrease with placebo	40% and 58%[b]	Decrease of 13% vs. to 8% increase with placebo
Number of new active lesions (Gd-enhanced MRI activity)	Reduction to 1.9 per patient vs. 4.3 per patient for placebo	62% and 33%[c]	Reduction to 2.0 per patient per scan vs. 3.0 per patient per scan for placebo
Increase in injection-site reactions, relative to placebo	48% vs. 8.5%	N.A.	60% vs. 12% with placebo
NAbs at two years	30%[d]	N.A.	N.A.
Frequency of administration/route	Every other day/SC	Weekly/IM	Weekly/SC, 22 mcg dose[e]

a. Full source citations appear in "Bibliography." Parenthetical entries identify the study from which these data were taken.
b. Patients were divided into two subgroups based on the baseline MRI T2-weighted lesion volume. Avonex treatment reduced lesion volume in both the lower and higher baseline T2 lesion volume subgroups.
c. Patients were divided into two subgroups based on the baseline absence or presence of at least one Gd-enhanced lesion. Avonex treatment reduced the number of new Gd-enhanced lesions in both subgroups.
d. Of these patients, 22.7% had no detectable NAbs later in the study.
e. Rebif is available in two dose strengths: 22 mcg and 44 mcg. Both doses are typically administered three times weekly. Only the 22 mcg dose administered once a week (i.e., administration at a much lower dose) was tested in this study.

BOD = Burden of disease; Gd = Gadolinium; IM = Intramuscular; MRI = Magnetic resonance imaging; N.A. = Not applicable; NAbs = Neutralizing antibodies; SC = Subcutaneous.

Note: Glatiramer acetate and natalizumab are not being investigated for early-stage MS.

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reduced the risk of developing CDMS by 16%. Betaseron treatment reduced the number of new lesions and the number and volume of gadolinium (Gd)-enhancing lesions. As is typical with Betaseron use, the most commonly reported adverse effects were injection-site reactions and flulike symptoms.

In an effort to improve efficacy, Bayer Schering Pharma and Berlex are conducting a multinational clinical trial to compare a high dose of Betaseron (500 mcg) with the current dose (250 mcg). The Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose (BEYOND) trial is a randomized, double-blind Phase III study that completed enrollment of more than 2,100 patients in July 2005. A previous small-scale study of 71 patients demonstrated that the 500 mcg dose of Betaseron was safe and well-tolerated. The BEYOND trial will compare not only the two doses of Betaseron with each other but also the efficacy of the high dose of the drug with that of glatiramer acetate. The study is slated to last two years; results are expected by the end of 2007.

Although Betaseron has been used predominantly in RR-MS and SP-MS with relapses (i.e., relapsing forms of MS), the drug has also been studied in PP-MS. A randomized, placebo-controlled Phase II study investigated the therapeutic efficacy of 250 mcg Betaseron every other day for two years (Montalban X, 2004). The primary end points were disability progression on the EDSS scale and lesion load as measured by MRI. Secondary end points included the Multiple Sclerosis Functional Composite (MSFC, which includes tests of ambulation, function, and cognition), T1 and T2 lesion load, and number of active lesions (Gd-enhancing).

Results at two years were mixed for Betaseron in PP-MS (Montalban X, 2004). The percentage of patients with confirmed disease progression as measured by EDSS at three months was similar in the Betaseron and placebo groups (27.8% versus 37.8% with placebo, not statistically significant). However, the study did find statistically significant differences, in favor of the Betaseron-treated group, in the MSFC, T1 and T2 lesion load, and number of active lesions (see Table 4-7). The significant treatment differences measured by MRI failed to translate to a clinically significant delay in the progression of PP-MS. Therefore, few neurologists prescribe Betaseron for this patient population.

In 2005, Betaseron had the lowest patient share among the IFN-βs because of its less-convenient dosing (once every other day) and ensuing high incidence of flulike symptoms. Modifications to the dose preparation and administration (room temperature storage capability, prefilled diluent syringes, autoinjectors) will only modestly increase convenience to patients. The agent will likely continue to be used in a patient population with very active disease and whose treatment decision is swayed more by efficacy than convenience. However, Betaseron will continue to hold limited share in the MS market (7% of market share in 2020), in part because of the drug's approval for the SP-MS and early-stage MS patient populations. Although Betaseron's patent expires in 2007 in the United States and 2008 in Europe and Japan, generic competition will not be a factor in the biologics market until regulatory authorities in these markets publish a framework for establishing bioequivalence, thus giving Betaseron additional years free

Table 4-7

Comparative Efficacy of Multiple Sclerosis Therapies in Clinical Trials for PP-MS, 2007

End Point	Betaseron	Avonex	Glatiramer acetate
Reduction in disease progression (Galetta S, 2002)[a]	No significant difference from placebo; trend toward greater reduction with Betaseron (Montalban X, 2004)	No significant difference from placebo (Leary SM, 2003)	No significant difference from placebo; trend toward greater reduction with glatiramer acetate (Wolinsky JS, 2004)
Reduction in MS Functional Composite (MSFC) worsening	Significant reduction vs. placebo	N.A.	N.A.
Lesion volume MRI activity at two years (BOD as measured with proton density T2-weighted MRI)	Significant reduction vs. placebo	No significant difference from placebo; trend toward greater reduction with Avonex	Volume increased over baseline; BOD decreased over baseline (same time frame)
Number of new active lesions (Gd-enhanced MRI activity)	Significant reduction vs. placebo	Few lesions developed; no difference from placebo	N.A.
NAbs at two years	N.A.	6% (n=1)	N.A.
Frequency of administration/route	Every other day/SC	Weekly/IM	Daily/SC

a. Full source citations appear in "Bibliography." Parenthetical entries identify the study from which these data were taken.

BOD = Burden of disease; Gd = Gadolinium; IM = Intramuscular; MRI = Magnetic resonance imaging; N.A. = Not applicable; NAbs = Neutralizing antibodies; PP-MS = Primary progressive multiple sclerosis; SC = Subcutaneous.

Note: Rebif and natalizumab are not being investigated for PP-MS.

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from generic competition. We expect generics to enter the European markets in 2008 and the U.S. market in 2012; generics will not be available in Japan during our forecast period. Given the small number of companies developing biogenerics, the technical and regulatory hurdles that these companies must overcome to develop biogenerics, and the expected limited use of Betaseron by 2020, generic Betaseron will only modestly affect the MS market.

Interferon Beta-1a (IM)

Biogen Idec's IFN-β-1a (Avonex) is the market leader in MS therapies; its sales represented slightly more than one-third of the total MS market in 2005. Avonex launched for RR-MS in 1996 in the United States, in 1997 in Europe, and in 2006 in Japan (see Table 4-4 for more information on Avonex in RR-MS clinical trials). The agent was also approved for early-stage MS in 2002 in Europe and in 2003 in the United States (see Table 4-8 for key facts on Avonex and Table 4-6 for more information on Avonex in early-stage MS clinical trials).

The efficacy of Avonex has been investigated in other MS patient populations with mixed results. The Phase III International Multiple Sclerosis Secondary Progressive Avonex Controlled Trial (IMPACT) investigated the efficacy of weekly 60 mcg Avonex injections (twice the dose used in RR-MS

Table 4-8

Key Facts: Avonex
Interferon Beta-1a (IM)
Launch Date: 1996 (US), 1997 (EU) 2006 (JA) for RR-MS; 2002 (EU), 2003 (US) for early-stage MS.
Brand Name and Marketer: Biogen Idec's Avonex.
Decision Resources' Expected Generic Entry: 2013 (US); 2008 (FR, GE, IT, SP, UK); post-2020 (JA).
Formulation and Dose: 30 mcg IM injection once weekly.
Mechanism of Action: The precise mechanism of action is unclear. IFN-β reduces T-cell migration across the BBB, suppresses T-cell proliferation, and alters the T-cell cytokine secretion repertoire in favor of anti-inflammatory cytokine response. Rebif and Betaseron have similar mechanisms of action.
Side Effects: The most common side effect associated with Avonex is flulike symptoms. Other side effects include depression/suicidal ideation, decreased peripheral blood counts, hypersensitivity reactions, and abnormal liver enzymes.
Development Activity: Biogen Idec is also conducting several MS trials studying the efficacy of Avonex in combination with other immunomodulating drugs, including the corticosteroid methylprednisolone, chemotherapeutic agents methotrexate and mycophenolate mofetil, the anticonvulsant topiramate (Ortho-McNeil's Topamax) and the statin simvastatin (Merck's Zocor).
Differentiating Features: Avonex's once-weekly dosing schedule is convenient for patients and advantageous in this market. The drug is now available in prefilled syringes for easier administration. Avonex is associated with fewer flulike side effects and a lower incidence of NAbs compared with other IFN-β drugs.
BBB = Blood-brain barrier; IFN = Interferon; IM = Intramuscular; NAbs = Neutralizing antibodies; RR-MS = Relapsing-remitting multiple sclerosis.
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patients) in patients with SP-MS and an EDSS score of 3.5-6.5 (Cohen JA, 2002). Avonex reduced clinically relevant disease progression but had no discernable effect on disability progression (see Table 4-5). An exploratory study was conducted to assess the therapeutic efficacy of Avonex in PP-MS patients over two years (Leary SM, 2003). However, the efficacy results were essentially negative, leading neurologists to rarely use Avonex in the PP-MS patient population (see Table 4-7).

Biogen Idec and Elan were investigating Avonex in combination with natalizumab, but clinical trials were halted when two patients taking the drug combination developed progressive multifocal leukoencephalopathy (PML). It is possible that combination use of these agents was the reason PML developed as opposed to natalizumab therapy alone. Indeed, there have been no reports of PML in connection with Avonex monotherapy. Nevertheless, Biogen Idec and Elan resubmitted their supplemental biologics license application (sBLA) to the FDA in September 2005, describing the results from the combination trial. It is highly unlikely that these two agents will be used in combination in medical practice because of the concerns over PML. Moreover, as some physicians point out, the combination was never slated to be promoted in some countries (such as the United Kingdom) because of the cost of combination therapy and the difficulty in getting biologics reimbursed.

Avonex's convenient once-weekly dosing and approval for early-stage MS are advantages in this market, particularly in newly diagnosed patients and

in patients with less aggressive forms of the disease. Avonex's IM route of administration and requirement for refrigeration are drawbacks for the drug, but to increase convenience, Biogen Idec has begun manufacturing prefilled syringes. Biogen Idec has countered Merck Serono/Pfizer's claim that their IFN-β-1a (Rebif) has superior efficacy by indicating that Avonex is associated with a lower incidence than Rebif of neutralizing antibodies (NAbs) and thus has better long-term efficacy.

Avonex will not experience generic competition for several years, contributing to its continued market dominance. Its patent is slated to expire in 2013 in the United States, and its patent expired in Europe and Japan in 2005. The European Medicines Agency (EMEA) was expected to draw up guidelines for IFN-βs in 2006, but no information on the status of these guidelines was available at the time of this writing. We expect the generic entry of Avonex in Europe to occur in 2008. In the United States, generics competition will not be a factor in the biologics market until regulatory authorities establish formats measuring bioequivalence, a step we do not expect to occur before 2010. We therefore expect generic Avonex to enter the U.S. market in 2013; generics will not be available in Japan during our forecast period. The uptake in generies will be modest; physician concerns over bioequivalence will moderately temper the push from reimbursement agencies to use generic forms.

Interferon Beta-1a (SC)

Interferon beta-1a (Merek Serono/Pfizer's Rebif) is a recombinant IFN-β therapy originally launched for RR-MS in 2002 in the United States and in 1999 in Europe (see Table 4-9). Rebif is available in two dose strengths: 22 meg and 44 mcg. In July 2006, the European Commission approved Rebif for use in patients who have experienced one demyelinating event and who have MRI scans tbat document this change (i.e., early-stage MS or clinieally isolated syndrome [CIS]).

At the time of Rebif's U.S. launch, Avonex was enjoying exelusivity as a result of its orphan-drug status; a Phase IV clinieal trial demonstrated Rebif's superior efficacy, which led to its approval by the FDA in 2002 and the overturning of Avonex's exelusivity, one year before Avonex's patent expiry in 2003. The Evidence for Interferon Dose-Effeet: European-North American Comparative Efficacy (EVIDENCE) trial, sponsored by Serono, compared the efficacy of Rebif with that of Avonex in RR-MS at the end of six months (EVIDENCE Study Group, 2001). A greater percentage of patients were relapse-free when administered Rebif (74.9%) than Avonex (63.3%), and the mean number of combined unique lesions per MRI scan was less in the Rebif group (0.7) than in the Avonex group (1.3, see Table 4-4). Many experts interviewed consider Rebif a first-line therapy because of the results of the EVIDENCE trial, which demonstrate that high-dose, more-frequent injections of IFN-β are more efficacious than lower-dose, less-frequent injections, such as is the case with Avonex.

In light of results from the EVIDENCE trial, Biogen Idec reasserted that because Avonex has a lower incidence of NAb formation, the drug's long-term efficacy will be superior to Rebif's; Merck Serono has responded by

Table 4-9

Key Facts: Rebif
Interferon Beta-1a (SC)
Launch Date: 2002 (US); 1999 (EU) for RR-MS. 2006 (EU) for early-stage MS.
Brand Name and Marketer: Merck Serono/Pfizer's Rebif.
Decision Resources' Expected Generic Entry: 2013 (US); 2013 (FR, GE, IT, SP, UK); N.A. (JA).
Formulation and Dose: 22 mcg or 44 mcg SC injection three times weekly.
Mechanism of Action: The precise mechanism of action is unclear. IFN-β reduces T-cell migration across the BBB, suppresses T-cell proliferation, and alters the T-cell cytokine secretion repertoire in favor of anti-inflammatory cytokine response. Avonex and Betaseron have similar mechanisms of action.
Side Effects: The most common side effects reported with Rebif use are flulike symptoms, chills, injection-site pain, and injection-site reaction. Other side effects include depression/suicidal ideation and abnormal liver enzymes.
Development Activity: In January 2007, Merck KGaA completed its acquisition of Serono, and the developmental fate of Rebif will be determined by this acquisition; Merck will likely continue further development of Rebif. The company is currently enrolling patients to study Rebif's effects in early-stage MS.
Differentiating Features: The EVIDENCE trial demonstrated Rebif's superior efficacy over Avonex. However, because Rebif has a more frequent dosing schedule than Avonex, Rebif is typically used once the patient's symptoms begin to worsen. Rebif is often chosen over Betaseron because its dosing frequency (three times weekly) is more convenient and easier to remember than Betaseron's (every other day).
BBB = Blood-brain barrier; IFN = Interferon; N.A. = Not applicable; RR-MS = Relapsing-remitting multiple sclerosis; SC = Subcutaneous.
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devising a reformulation of Rebif that has fewer injection-site reactions and reduced NAb formation. One-year data from a two-year Phase III trial demonstrated that the reformulated Rebif, administered at 44 mcg three times weekly, resulted in a threefold decline in injection-site reactions over the original form (29.6% compared with 84% in the EVIDENCE study). The percentage of injection-site reactions that occurred with reformulated Rebif is similar to that of Avonex in the EVIDENCE trial (28%), a marked improvement for Rebif, particularly because it is dosed more frequently than Avonex. Data from this trial also demonstrate that 2.5% of patients given reformulated Rebif developed persistent NAbs at 48 weeks, compared with 58% of patients given original Rebif and 14% of Avonex patients in the earlier EVIDENCE trial (Merck Serono, press release, September 28, 2006). These data bode well for Rebif, and consistently lower levels of injection-site reactions and persistent low levels of NAbs at the two-year point will prove favorable for continued use of the drug.

Merck Serono submitted an sBLA to the FDA in April 2006 for the new formulation of Rebif; this reformulation is also under review with the EMEA. In February 2007, the FDA asked Merck Serono for additional information on reformulated Rebif, although it is unclear what information the FDA requires. We expect that the new formulation of Rebif will launch in 2007.

Rebif has also been investigated in SP-MS and has demonstrated some efficacy in this patient population, particularly with patients who continue to relapse. The Secondary Progressive Efficacy Trial of Interferon-β-1a in

MS Study (SPECTRIMS) was a three-year, double-blind, randomized Phase IV trial comparing 22 mcg and 44 mcg doses of Rebif three times per week with placebo (Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results, 2001; Li DK, 2001) (see Table 4-5). Results demonstrated that although Rebif had no statistically significant effect on progression of disability as measured on the EDSS, the drug reduced the number of relapses seen in those SP-MS patients who still experienced relapses. These data support the theory that IFN-β is more effective in treating SP-MS patients who experience continued relapses because of continued inflammation in their CNS but not those patients who have ceased to have an inflammatory component to their disease. An amendment to the drug's labeling to include treatment in SP-MS patients has been submitted in several countries.

Rebif has shown promise as a therapy for early-stage MS. The Early Treatment of Multiple Sclerosis (ETOMS) trial investigated whether 22 mcg of Rebif once weekly (i.e., at much lower doses than typically administered) for two years (Comi G, 2001a) could slow progression to CDMS in patients who had experienced a first clinical episode suggestive of demyelinating disease. Rebif treatment appeared to delay the progression to CDMS (see Table 4-6), lending support for the use of Rebif for the early treatment of MS. However, because the drug is associated with the development of NAbs over time, some physicians interviewed are wary of starting CIS patients on Rebif too early because of the possibility that the patient may develop Nabs and the efficacy of the drug would be dampened.

The reformulation of Rebif may reverse this view. Given the positive one-year Phase III data of reformulated Rebif, Merck Serono initiated the Rebif Flexible Dosing in Early MS (REFLEX) trial in December 2006 to examine the efficacy of reformulated Rebif in delaying the time to conversion to CDMS, as assessed by the McDonald criteria. In this randomized, placebo-controlled, double-blind study, patients will receive 44 mcg SC injection of reformulated Rebif either three times a week (Rebif's current dosing schedule) or once a week. The once-a-week dosing regimen is comparable to that of Avonex, and it is likely that Merck Serono is testing this dosing schedule to compete with Avonex for the early-stage MS patient population. In addition to examining the time to conversion to CDMS (the primary end point), the study will assess MRI end points, clinical relapses, disability progression, and cognitive function (the latter is an end point that no drug developer has evaluated thus far and may prove to be a significant marketing advantage for Merck Serono). In addition, the REFLEX study will measure retinal axonal thickness (as an evaluation of axonal loss) and attempt to identify genetic biomarkers associated with RR-MS. The study is slated to last for two years.

Merck Serono is also comparing Rebif with the APL glatiramer acetate in a two-year, head-to-head Phase IV trial comparing the efficacy of 44 mcg Rebif three times weekly with that of 20 mg/day glatiramer acetate. Results from the trial are expected in 2007. This trial is the first head-to-head study comparing the relative efficacy of an IFN-β and glatiramer acetate. The market uptake of glatiramer acetate has been robust—particularly in Europe (specifically France, Italy, and Spain)—because of the drug's benign side-

effect profile, yet physicians question its efficacy. If Merck Serono can prove that Rebif possesses superior therapeutic efficacy over glatiramer acetate, sales may improve, not only for Rebif but also for other IFN-βs. However, a new dosage of glatiramer acetate (40 mg) may confound results from this trial because Merck Serono's Phase IV trial is comparing the efficacy of Rebif with the original dosage of glatiramer acetate (20 mg).

Rebif's EVIDENCE trial data show efficacy superior to that of market leader Avonex, but because of its increased dosing frequency and high incidence of injection-site reactions and NAbs, use of Rebif is typically delayed until a patient's symptoms begin to worsen. On the other hand, Rebif is often selected over the other high-frequency IFN-β, Betaseron, because Rebif has an easier dosing schedule (three times weekly) compared with every other day for Betaseron. Another advantage of Rebif is that it comes in a prefilled syringe rather than requiring reconstitution from a powder. Reformulated Rebif thus far appears to alleviate some of the more detrimental aspects of the drug, namely injection-site reaction, which will likely increase use of this drug if its improved safety continues throughout Phase III trials.

In January 2007, Merck KGaA completed its acquisition of Serono, which it renamed Merck Serono, and the developmental fate of Rebif will depend on Merck KGaA. We expect development of reformulated Rebif to continue because of the encouraging clinical trial results regarding reformulated Rebif thus far. We expect that reformulated Rebif will temper the decline of this franchise, which will occur as a result of competition from emerging therapies and biogenerics.

Altered Peptide Ligands

Glatiramer Acetate

Glatiramer acetate (Teva Pharmaceuticals' Copaxone) is the only APL approved to treat MS. It was initially launched in the United States in 1997 and in Europe in 2001 for the treatment of RR-MS (see Table 4-4 for more information on glatiramer acetate in RR-MS clinical trials). The results of a European/Canadian Phase IV MRI study demonstrated that glatiramer acetate reduces the formation of new MS lesions in RR-MS, prompting the FDA to approve expanded labeling of glatiramer acetate to reflect this additional clinical evidence. Table 4-10 lists key facts about glatiramer acetate.

In 2004, Teva received approval in Europe and the United States for a prefilled-syringe formulation that may be stored for seven days at room temperature. Teva and Lundbeck were investigating an oral formulation of glatiramer acetate in the United States, but development was suspended in March 2006 after two Phase II trials failed to demonstrate efficacy. Teva is continuing to explore other oral dose formulations.

Glatiramer acetate is also in development for other indications. A Phase II trial is examining glatiramer acetate's efficacy in amyotrophic lateral sclerosis (ALS), and the drug is in preclinical studies for other, unspecified neurodegenerative disorders.

Table 4-10

Key Facts: Glatiramer Acetate
Glatiramer Acetate
Launch Date: 1997 (US); 2001 (EU) for RR-MS.
Brand Name and Marketer: Teva Pharmaceutical Copaxone.
Decision Resources' Expected Generic Entry: 2014 (US); 2015 (FR, GE, IT, SP, UK); N.A. (JA).
Formulation and Dose: 20 mg SC injection once daily.
Mechanism of Action: The precise mechanism of action is unclear. Glatiramer acetate inhibits T-cell activation and alters the T-cell cytokine secretion repertoire in favor of anti-inflammatory cytokine response. It may also play a neuroprotective role by inducing T-cell secretion of the neurotrophic factor BDNF.
Side Effects: The most common side effects reported are injection-site reactions and injection-site pain. Less-common side effects that occurred more frequently with glatiramer acetate include chest pain and vasodilation.
Development Activity: Teva is investigating oral formulations of glatiramer acetate. Teva is also conducting Phase III trials examining the efficacy of a double-dose (40 mg) of glatiramer acetate for RR-MS. Results from a Phase II trial demonstrated increased efficacy with the higher dose without a worsening of side effects.
Differentiating Features: Glatiramer acetate has fewer severe side effects than other currently available MS therapies, including fewer flulike side effects. Although it requires daily administration, the drug is now available in convenient prefilled syringes that can be stored for up to 7 days at room temperature.
BDNF = Brain-derived neurotrophic factor; N.A. = Not applicable; RR-MS = Relapsing-remitting multiple sclerosis; SC = Subcutaneous.
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Glatiramer acetate is a synthetic chain of four amino acids—L-alanine, L-lysine, L-glutamic acid, and L-tyrosine—whose chemical structure resembles that of the myelin basic protein (MBP) molecule (Dhib-Jalbut S, 2003). MBP is an antigen believed to play a role in the pathogenesis of MS. The means by which glatiramer acetate impedes the autoimmune attack in MS is unclear, but several theories of the drug's mechanism of action have been advanced. Glatiramer acetate engages the T-cell receptor (TCR) and functions as an antagonist or partial agonist of the receptor. As a TCR antagonist, glatiramer acetate inhibits T-cell activation; as a partial agonist to the TCR, glatiramer acetate activates only a subset of T-cell-signaling events, thus altering the normal inflammatory pathway. Glatiramer acetate may also induce naive, or nonactivated, T cells to become anti-inflammatory T_H2 cells instead of proinflammatory T_H1 cells (immune deviation) (Duda PW, 2000b; Kappos L, 2000), which then enter the CNS and help reduce the inflammatory process that can cause demyelination (Dhib-Jalbut S, 2003). Unlike IFN-β therapies, glatiramer acetate probably does not affect the movement of T cells across the BBB into the CNS (Yong VW, 2002). Glatiramer acetate may also play a neuroprotective role in treating MS. Glatiramer-acetate-specific T_H2 (and T_H1) cells may produce brain-derived neurotrophic factor (BDNF), a potent neurotrophic factor that has neuroprotective and repair characteristics in the CNS (Ziemssen T, 2002). However, it remains to be determined whether (and to what degree) such a neuroprotective effect can be demonstrated in clinical practice.

Teva is seeking to expand glatiramer acetate's labeling to include other MS populations, notably SP-MS and PP-MS patients. The company initiated

the Phase II PROMISE (Copaxone in Primary Progressive Multiple Sclerosis) trial to evaluate the efficacy of glatiramer acetate in delaying disease progression (based on the EDSS) in SP-MS and PP-MS patients (see Table 4-7). This study was terminated prematurely because of a lack of therapeutic efficacy; the reduction in disease progression did not reach a statistically significant difference between the two treatment groups (17.6% reduction with glatiramer acetate treatment compared with 25.5% reduction with placebo treatment). Although glatiramer acetate does not appear to be effective in the treatment of PP-MS, a post hoc analysis of the available data from the PROMISE trial found that male PP-MS patients treated with glatiramer acetate had significantly slower rates of clinical progression compared with placebo-treated patients (Wolinsky JS, 2004; Wolinsky JS, 2007). Teva has not announced plans to reinitiate the PROMISE trial.

Glatiramer acetate is also being investigated in early-stage MS. In 1995, Teva formed an alliance with Sanofi-Aventis to market and distribute glatiramer acetate in North America; Teva maintained rights to the rest of the world. Although the marketing role was transferred wholly to Teva in 2001, Sanofi-Aventis continues to distribute glatiramer acetate in North America. In September 2004, Sanofi-Aventis initiated a Phase III trial to study the effect of glatiramer acetate in early-stage MS patients in Europe. The study was ongoing as of 2005 (Sanofi-Aventis 2005 annual report).

Teva is investigating the therapeutic efficacy of doubling doses of glatiramer acetate to 40 mg. Results from a Phase II trial in 90 RR-MS patients were presented at the American Academy of Neurology (AAN)'s 58th annual meeting (April 1-8, 2006, San Diego). Patients taking the 40 mg dose showed a 38% greater reduction in lesions compared with patients taking the 20 mg dose. In addition, patients on the higher dose had a 77% reduction in their average annual relapse rate compared with a 62% reduction in patients on the 20 mg dose. Side effects did not worsen in patients on the higher dose. Teva is now enrolling patients in a Phase III trial with the 40 mg dose; results are expected in 2008.

Glatiramer acetate is rapidly becoming a first-line therapy in RR-MS. Outside the United States, glatiramer acetate is the fastest-growing RR-MS therapy; its sales in the United States are also steadily increasing (Teva Pharmaceuticals, press release, October 31, 2006). Glatiramer acetate benefits from fewer severe side effects—notably, fewer flulike side effects—than the IFN-βs. Although it must be administered daily, its availability in prefilled syringes and room temperature storage capability (for up to seven days) improve convenience. Glatiramer acetate will continue to hold patient and market share through 2020, despite increasing competition from emerging agents and biogenerics when they become available in 2014.

Monoclonal Antibodies

Natalizumab

Natalizumab (Biogen Idec/Elan's Tysabri) was the first antibody launched for the treatment of MS (see Table 4-11). It was launched in the United States in November 2004 for RR-MS. However, Biogen Idec and Elan voluntarily withdrew natalizumab from the market in February 2005 because two

Table 4-11

Key Facts: Natalizumab
Natalizumab
Launch Date: 2004 (US), 2006 (EU), 2012 (JA) for relapsing forms of MS.
Brand Name and Marketer: Biogen Idec/Elan's Tysabri.
Decision Resources' Expected Generic Entry: 2014 (US); 2015 (FR, GE, IT, SP, UK); post-2020 (JA).
Formulation and Dose: 300 mg IV once-monthly infusion.
Mechanism of Action: Natalizumab is a humanized MAb that targets the α4-integrin protein (also known as the CD49/CD29 or very late antigen-4 [VLA-4]) expressed on the surface of T cells and macrophages; blocking this protein is expected to prevent T cells from migrating into the brain, thus reducing or eliminating the T-cell-mediated inflammatory response.
Side Effects: Opportunistic infections, including PML, a rare but severe and potentially life-threatening viral infection; hypersensitivity reactions; mild side effects included headache, fatigue, and limb and joint pain.
Development Activity: Natalizumab was launched in the United States in November 2004. In February 2005, Biogen Idec and Elan voluntarily withdrew natalizumab from the market after two patients participating in clinical trials with natalizumab developed PML. Clinical trials with natalizumab were also halted while the companies reviewed safety data. Three cases of PML were found, and two of these cases were fatal. Natalizumab was relaunched in July 2006 in the United States with a black box warning about the risk of developing PML and a requirement for all patients to enroll in a risk management plan, the TOUCH Prescribing Program. Also in July 2006, natalizumab was approved in Europe for RR-MS.
Differentiating Features: Natalizumab has a novel mechanism of action compared with other current disease-modifying therapies for MS. Natalizumab has shown significant efficacy in reducing relapse rates, disability progression (as assessed by EDSS), and the number of new or enlarging T2-weighted and Gd-enhancing lesions, which makes it attractive for patients who are refractory to or intolerant of IFN-β therapies. However, the risk of developing PML will prevent first-line use of this drug. It will likely be administered to patients with aggressive forms of RR-MS.
EDSS = Expanded Disability Status Scale; Gd = Gadolinium; IFN = Interferon; IV = Intravenous; MAb = Monoclonal antibody; PML = Progressive multifocal leukoencephalopathy; RR-MS = Relapsing-remitting multiple sclerosis.
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patients participating in natalizumab clinical trials developed fatal PML. PML is a rare and potentially fatal demyelinating disease caused by an opportunistic infection of the CNS by the JC virus (JCV). The companies also halted ongoing clinical trials in order to review safety data.

Although clinical trials were on hold, a third case of PML was diagnosed in a patient with Crohn's disease (CD) who was taking natalizumab. Three cases of PML were confirmed in total, and two of the cases proved fatal. It is unclear whether PML developed in these patients as a direct result of natalizumab therapy because, in the cases of the MS patients, natalizumab was taken in combination with Avonex; no cases of PML were reported in patients receiving either natalizumab or Avonex monotherapy. The CD patient who developed PML was taking natalizumab as a monotherapy but had recently been administered an immunosuppressant (azathioprine). It is possible that a combination of immune-modifying drugs, whether concomitant (natalizumab and Avonex) or consecutive (immunosuppressants, then natalizumab), results in such a severe immunocompromised state that opportunistic infections like PML are more likely to develop.

The companies completed their safety review in August 2005 and resubmitted an sBLA to the FDA in October 2005. The agency gave the application priority review. The FDA's Peripheral and Central Nervous System Drugs Advisory Committee unanimously recommended that natalizumab be reintroduced on the U.S. market and voted, by a narrow margin, that the drug be used first-line as a monotherapy in RR-MS patients who continue to relapse on, or who are not tolerant of, other currently available immunomodulators; patients who have aggressive RR-MS; patients who were not immunocompromised; and patients who enrolled in the Biogen Idec Risk Minimization Action Plan (RiskMAP) registry, termed the Tysabri Outreach: Unified Commitment to Health (TOUCH) Prescribing Program (26th SG Cowen Elan Company Presentation, March 9, 2006). The TOUCH program was instituted to monitor patients who receive natalizumab treatment for incidents of PML or other serious adverse effects that may develop. Natalizumab was relaunched in the United States in July 2006. Natalizumab was approved in Europe for the first time during the same month.

Biogen Idec and Elan were also collaborating on developing natalizumab for immune and inflammatory conditions other than MS, including CD and rheumatoid arthritis (RA). Natalizumab is preregistered in Europe for CD and in Phase III trials in the United States for the same indication. The companies have suspended Phase II trials of natalizumab in RA patients, citing safety concerns and a lack of demonstrated efficacy.

Natalizumab is a humanized monoclonal antibody (MAb) directed against the alpha-4 (α4)-integrin expressed on the surfaces of T cells and macrophages; blocking of the α4-integrin by a MAb should prevent activated T-cell entry through the BBB and into the CNS. Alpha-4-integrin is part of the alpha-4 beta-1 (α4β1) and alpha-4 beta-7 (α4β7) integrin complexes. Binding of α4β1 integrin to vascular cell adhesion molecule-1 (VCAM-1) on the lining of cerebral blood vessels is the initial step in T-cell migration across the BBB. By blocking α4β1 integrin/VCAM-1 interaction, natalizumab is expected to prevent the binding of T cells to the endothelium and thus their migration into the brain, thereby reducing or eliminating T-cell-induced inflammation seen during an MS relapse and the subsequent destruction of myelin.

Clinical trial data have demonstrated natalizumab's remarkable efficacy as an RR-MS therapy. Table 4-12 presents highlights of these clinical trials. The Phase III Antegren Safety and Efficacy in RR-MS (AFFIRM) trial examined the efficacy of 300 mg monthly intravenous (IV) doses of natalizumab in delaying disease progression. (Note that natalizumab's original brand name was Antegren. The drug was renamed Tysabri in 2004 at the request of the FDA to avoid prescribing confusions, possibly with Millennium Pharmaceuticals' Integrilin.) A primary end point for this study included the EDSS score. For patients with an EDSS score of 1 or more at the initiation of the study, disability progression was defined as a one-point increase in EDSS score sustained for 12 weeks. For patients with an EDSS score of 0, disability progression was defined as a sustained 1.5-point increase in EDSS score over 12 weeks. Another primary end point was relapse rate at one and two years. Secondary end points included the rate and number of relapses (see Table 4-4 for more information on natalizumab in RR-MS clinical trials).

Table 4-12

Natalizumab Pivotal Trial Highlights

	AFFIRM (Monotherapy)		SENTINEL (In Combination with Avonex)	
End Point	1-Year Data	2-Year Data	1-Year Data	2-Year Data
Annualized relapse rate	0.27 with natalizumab vs. 0.78 with placebo	0.23 with natalizumab vs. 0.73 with placebo	0.38 with natalizumab/Avonex vs. 0.81 with Avonex alone	0.34 with natalizumab/Avonex vs. 0.75 with Avonex alone
Reduction in relapse rate	68%	68%	54%	55%
Percentage of relapse-free patients	80% with natalizumab vs. 60% with placebo	72% with natalizumab vs. 46% with placebo	72% with natalizumab/Avonex vs. 51% with Avonex alone	61% with natalizumab/Avonex vs. 37% with Avonex alone
Reduction in sustained disability scores	N.A.	42%	N.A.	24%
Probability of progression	N.A.	17% with natalizumab vs. 29% with placebo	N.A.	23% with natalizumab/Avonex vs. 29% with Avonex alone
Reduction in the accumulation of new or enlarging T2 lesions over two years	N.A.	83%	N.A.	83%
Mean number of new or enlarging T2 lesions	1.2 with natalizumab vs. 6.1 with placebo	1.9 with natalizumab vs. 11 with placebo	0.5 with natalizumab/Avonex vs. 2.4 with Avonex alone	0.9 with natalizumab/Avonex vs. 5.4 with Avonex alone
Reduction in Gd-enhancing lesions	92%	92%	87%	89%
Mean number of Gd-enhancing lesions	0.1 with natalizumab vs. 1.3 with placebo	0.1 with natalizumab vs. 1.2 with placebo	0.1 with natalizumab/Avonex vs. 0.8 with Avonex alone	0.1 with natalizumab/Avonex vs. 0.9 with Avonex alone

AFFIRM = Antegren Safety and Efficacy in RR-MS; Gd = Gadolinium; N.A. = Not applicable; SENTINEL = Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis.

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Data from the AFFIRM study demonstrate that natalizumab met its primary and secondary end points (Polman CH, 2006). At two years, natalizumab reduced disease progression by 42%. Relapse rates at one year dropped by 68%, a percentage that was maintained at the two-year point, indicating that the drug can sustain its level of efficacy over time. Lesion volume, as measured by proton density T2-weighted MRI, was reduced by 83% compared with placebo. The number of new active lesions fell 92% relative to control, as assessed by Gd-enhanced MRI.

Natalizumab was also investigated in another Phase III trial, Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1-a in Patients with Relapsing-Remitting Multiple Sclerosis (SENTINEL), to examine whether its efficacy in combination with Avonex is superior to that of Avonex alone in delaying disease progression and reducing the rate of clinical

relapses (Rudick RA, 2006). The primary end point of this two-year study was the change in EDSS score after two years. The one-year interim primary end point was reduction in relapse rate.

Two-year results from the SENTINEL study showed that the combination of natalizumab and Avonex reduced disability progression and sustained the reduction in lesion size and the number of new lesions over Avonex monotherapy (see Table 4-12) (Rudick RA, 2006). Disability progression was reduced by 24% in patients who reeeived combination therapy compared with patients who reeeived Avonex alone. Relapse rates in patients reeeiving natalizumab in combination with Avonex were reduced by 54% compared with Avonex monotherapy (mean relapse rate/patient at two years: 0.34 with combination therapy compared to 0.75 with Avonex alone, $p<0.001$). A larger percentage of patients also remained relapse-free when administered the combination therapy (72%) than Avonex alone (51%), while the number of new or enlarging T2- and Gd-enhancing lesions was reduced more in patients treated with the combination therapy (72%) compared with Avonex monotherapy (43%). In addition, 96% of patients on combination therapy had no new Gd-enhancing lesions compared with 75% of patients treated with Avonex alone.

In both the AFFIRM and SENTINEL studies, persistent levels of NAbs against natalizumab were detected, suggesting that the efficacy of the drug could wane over time in some patients. Six percent of patients in the AFFIRM study and 12% of patients in the SENTINEL study who received natalizumab therapy developed NAbs to natalizumab (Polman CH, 2006; Rudick RA, 2006). The presence of these antibodies resulted in lower efficacy and increased infusion-related side effects, which could be severe at times. The FDA Advisory Committee suggests that patients be screened for NAbs if natalizumab's efficacy declines or if side effects occur. The committee further recommends that natalizumab treatment be interrupted if NAbs are detected because natalizumab's therapeutic efficacy is reduced in these patients and hypersensitivity reactions may occur more often in these patients. These antibodies developed within 12 weeks of treatment, so it may be possible to detect these patients early and stop their treatment in order to alleviate safety concerns and poor therapeutic efficacy associated with continued use of the drug.

Side effects of natalizumab were similar in both the AFFIRM and SENTINEL trials at one year. Overall, it was well tolerated; the most frequent adverse effects were fatigue and allergic reactions. Hypersensitivity reactions occurred in 4% of patients receiving natalizumab, and 1% of these reactions were serious (Polman CH, 2006). However, safety data at two years reveal the development of PML in two patients treated with natalizumab and Avonex combination therapy, although no cases of PML were reported with natalizumab monotherapy.

The increased risk of developing PML has significantly affected natalizumab's commercial prospects. Prior to its 2004 launch, it was widely anticipated to be a major player in the MS therapy market because of its excellent efficacy at delaying disease progression and reducing relapse rates. Natalizumab's unique mechanism of action and its more-convenient dosing

schedule (once-monthly infusion) also contributed to its promising market prospects. However, the current black box warning concerning the increased risk of PML, in addition to expensive screening and monitoring at approved infusion centers required to ensure absence of PML, will prevent natalizumab from becoming a first-line therapy for RR-MS. Instead, it will be reserved for those patients who have failed IFN-β and glatiramer acetate therapy, those patients with aggressive forms of RR-MS, and those patients who have reached their lifetime dose limit of mitoxantrone and are left with few therapeutic options.

In the United States, a risk management plan has been implemented to monitor natalizumab use and the development of any opportunistic infections like PML. All patients who receive natalizumab, as well as all prescribers, infusion centers, and pharmacies that are involved in natalizumab distribution and administration, are required to enroll in the TOUCH Prescribing Program. It is hoped that this extensive monitoring program will promote awareness of PML for both patients and physicians and will permit tracking of patients' natalizumab usage and any cases of PML that may develop.

No official risk management plan exists in Europe, so hospitals and even individual physicians are responsible for monitoring patients who receive natalizumab. Experts interviewed state that European natalizumab patients are not required to enroll in a registry, although the drug's manufacturers are encouraging implementation of some form of risk management. Indeed, Biogen Idec has instituted a global monitoring plan, the Tysabri Global Observation Program for Safety (TYGRIS). This program will follow 5,000 natalizumab patients for five years to assess the risks of PML, but it does not have the strict regulations of the U.S. TOUCH program.

Since its relaunch in July 2006, uptake of natalizumab in the United States has been limited by the requirement that all physicians, patients, and infusion sites enroll in the TOUCH Prescribing Program. Nearly 1,000 individual physicians or infusion locations (representing 40-50% of all U.S. physicians and infusion centers that treat most MS patients) have received training in the TOUCH program thus far. Approximately 1,700 of the 4,500 MS patients currently enrolled in the TOUCH program had received their first natalizumab infusion as of October 2006 (Elan Third Quarter Financial Report, October 25, 2006). Biogen Idec announced that as of February 2007, nearly 10,000 patients worldwide had been prescribed natalizumab.

In Europe, where it was approved for the first time in July 2006, natalizumab uptake has been very slow. According to Elan's Third Quarter Financial Report, only 500-600 European patients have received the drug. The majority of neurologists interviewed express great concern about natalizumab's side effects; many neurologists are not widely prescribing natalizumab because they are waiting to see if additional cases of PML develop. One Italian neurologist states, "We will have to try [with] natalizumab to be very careful at the beginning, but if the prevalence of side effects of PML will be the same as in the trial populations, I don't think it will be a major concern, especially because now we are expecting it, so we are ready to face the problem and to monitor patients more accurately." Most experts interviewed state that they will prescribe natalizumab, albeit to a limited number of patients, although a

few neurologists interviewed state that they will not prescribe natalizumab at all because of the side effects.

Natalizumab is available in several European countries, including Germany and the United Kingdom, and the majority of patients who have received natalizumab to date are from Germany. Physicians in the United Kingdom are waiting until the National Institute for Health and Clinical Excellence (NICE) makes a recommendation on the drug, which is expected to occur in the spring of 2007. The drug was referred to NICE's single technology appraisal (STA) process in August 2006; this process accelerates a drug's assessment period from two years to six months (National Institute for Health and Clinical Excellence, 2006). Natalizumab is slated to become available in additional European markets through the first half of 2007 as Biogen Idec and Elan work out reimbursement strategies with individual countries. Even with reimbursement strategies in place, natalizumab will likely garner less than 10% of RR-MS patient share in Europe over the course of our 2005-2020 forecast period.

Despite the FDA Advisory Committee's recommendation that natalizumab be used as a first-line therapy, the FDA did not follow the committee's recommendation; instead, it approved natalizumab as a non-first-line therapy. The drug will likely be used in no more than 10% of the RR-MS patient population in the United States and Europe over the course of our forecast period. We expect natalizumab to launch in Japan in 2012, where it will be used in no more than 8% of the RR-MS patient population during our forecast period. The high cost of this drug will also contribute to its limited use in MS. Natalizumab was priced aggressively high on its initial launch (more than $55 per day), and Biogen Idec and Elan increased the U.S. price of natalizumab by 21% over its original launch price upon the drug's relaunch. The companies cite the additional costs of implementing the TOUCH program as the reason for the price increase. Natalizumab's price in European markets and Japan is similar to current U.S. prices. Because of these obstacles (the possibility of fatal side effects, the FDA's recommendation, the drug's high cost, physician wariness at prescribing the drug, and the monitoring program requirement), natalizumab will not achieve its originally anticipated blockbuster status but will provide an efficacious alternative therapy for patients with aggressive RR-MS and for RR-MS patients who are not adequately controlled by other therapies.

Chemotherapeutics

Overview

Immunosuppressive agents have been launched for cancer treatment, but their broad immunosuppressant properties have also been found useful in the treatment of aggressive forms of RR-MS and SP-MS (mostly as adjunct therapy to IFN-β or glatiramer acetate treatment) and in patients refractory to IFN-β or glatiramer acetate treatment. Immunosuppressive agents' efficacy is thought to result from their ability to increase the production of anti-inflammatory cytokines and/or reduce the production of proinflammatory cytokines, which helps slow the progression of MS. Their side effects are

more severe than those of immunomodulators; as such, their use is limited to aggressive forms of MS.

Only the immunosuppressant mitoxantrone (Merck Serono/Amgen's Novantrone) has undergone clinical trials in MS patients and been approved for the treatment of worsening RR-MS and SP-MS. Mitoxantrone was also the first drug approved in the United States for the treatment of SP-MS (the drug is not approved for SP-MS in Europe or Japan). Because of its proven therapeutic efficacy, mitoxantrone is considered first-line therapy among immunosuppressants. However, the drug has severe side effects, notably cardiotoxicity, and as such has a lifetime cumulative dose limit. Once this lifetime dose limit is reached, neurologists turn to off-label use of other immunosuppressants, such as mycophenolate mofetil (MMF, Roche's CellCept), methotrexate (Wyeth's Rheumatrex, generics), cyclophosphamide (Bristol-Myers Squibb's Cytoxan, generics), and azathioprine (GlaxoSmithKline's Imuran, generics); all of which have limited efficacy. MMF is not currently approved for MS treatment in the United States or Europe but is being investigated for it. We discuss mitoxantrone and MMF at length later in this section; use of the other immunosuppressants is limited in MS and therefore they are not discussed here. (For details on these drugs, see the following report: Multiple sclerosis. Decision Resources, Inc. *Pharmacor; Cognos.* Study #3, 2006.)

Mechanism of Action

Immunosuppressive drugs act by preventing the proliferation of T cells, which occurs upon their activation. However, because these drugs act nonspecifically on any dividing cell, including normally dividing cells, their side effects are significantly more severe than those of immunomodulatory drugs. Side effects include the risk of developing opportunistic infections and malignancies (e.g., acute myelogenous leukemia [AML]). In addition to disrupting T-cell proliferation, MMF prevents the glycosylation of adhesion molecules normally required for lymphocyte infiltration and recruitment to sites of inflammation, raising the possibility of developing opportunistic infections similar to those seen with natalizumab (Allison AC, 2000).

Formulation

Immunosuppressive agents are generally given in an outpatient format administered by IV. MMF, methotrexate, and azathioprine are available in an oral formulation.

Mitoxantrone

Mitoxantrone received FDA approval in 2000 to treat SP-MS, PR-MS, and worsening RR-MS, thereby becoming the only chemotherapeutic agent approved for MS in the United States (see Table 4-13). Indeed, guidelines published by the AAN suggest that mitoxantrone may have a beneficial effect on disease progression in MS patients who are deteriorating clinically or are refractory to other treatments (Goodin DS, 2003). Mitoxantrone is in Phase III trials for MS in Europe, but no development has been reported in Japan.

Table 4-13

Key Facts: Mitoxantrone
Mitoxantrone
Launch Date: 1988 (US); 1985 (EU); 1987 (JA) for cancer treatment. Approved for MS in 2000 (US); used off-label in other markets.
Brand Name and Marketer: Merck Serono/Amgen's Novantrone, generics.
Decision Resources' Expected Generic Entry: Patent expired; generics currently available.
Formulation and Dose: 8-12 mg/m^2 (IV infusion) every three months. Mitoxantrone has a lifetime dose limit of 140 mg/m^2. The average MS patient can receive 2-3 years of treatment.
Mechanism of Action: Prevents the proliferation of T cells. However, mitoxantrone acts nonspecifically on all dividing cells, resulting in severe side effects.
Side Effects: Cardiotoxicity, which requires cardiac, blood count, and liver monitoring; increased risk of opportunistic infections; risk of developing secondary AML.
Development Activity: Mitoxantrone received FDA approval in 2000 for use in SP-MS, PP-MS, and worsening RR-MS, thereby becoming the only chemotherapeutic agent approved for MS in the United States. Mitoxantrone is in Phase III trials in Europe, but no development in MS has been reported in Japan.
Differentiating Features: Mitoxantrone is the only immunosuppressant indicated for SP-MS. It also has some efficacy in aggressive forms of RR-MS. Its side-effect profile, particularly the risk of developing secondary AML, and its lifetime dose restriction have limited its use.
AML = Acute myelogenous leukemia; IV = Intravenous; PP-MS = Primary progressive multiple sclerosis; RR-MS = Relapsing-remitting multiple sclerosis; SP-MS = Secondary progressive multiple sclerosis.
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Source: Decision Resources, Inc.

One pivotal clinical trial was conducted examining the efficacy of mitoxantrone in worsening RR-MS and SP-MS. The Mitoxantrone in Multiple Sclerosis (MIMS) trial compared two strengths of mitoxantrone (5 mg/m^2 and 12 mg/m^2) with placebo (Hartung HP, 2002). The primary end point was a composite score of five clinical measures: change in EDSS, change in ambulation index, number of relapses treated with corticosteroids, time to first relapse, and change in standard neurological status; the secondary end point was improvement on MRI scans of lesion load.

Results of the MIMS study demonstrated a significant treatment effect for 12 mg/m^2 mitoxantrone across all five clinical measures. Patients on the higher dose experienced a 68% reduction in the number of relapses and a significant delay in relapses compared with placebo (see Table 4-4 for more details on the MIMS study). The higher dose of the drug also slightly improved or slowed disability progression. The change in ambulation index score was greater in placebo-treated patients (0.77 points) than in mitoxantrone-treated patients (0.30 points). In the standardized neurological status, placebo-treated patients worsened by 0.77 points and mitoxantrone-treated patients improved by 1.07 points. Mitoxantrone also reduced the mean number of new and active lesions compared with placebo. Clinical benefits for patients treated with 5 mg/m^2 mitoxantrone were less robust. The FDA approved mitoxantrone for MS in 2000, before results from the pivotal trial were published, prompting some physicians interviewed to claim that the approval was not grounded in solid peer review.

Data presented in abstract form suggest that mitoxantrone may also prevent disease progression in PP-MS. In an open-label trial, 64 patients with PP-MS were treated with mitoxantrone either monthly for six months or every three months for up to 24 months (Coustans M, 2003). From baseline to the end of the first year, 19% of patients had a one-point worsening in their EDSS, while 24% of patients improved. From the baseline assessment to the end of the second year, 34% of patients deteriorated and 24% had a one-point improvement in their EDSS. When compared with the natural history of MS patients, these data demonstrate a 50% reduction in the yearly one-point EDSS deterioration rate.

Mitoxantrone has an advantage over other chemotherapeutic agents in that it is the only immunosuppressive agent currently indicated for the treatment of SP-MS. The drug also appears to have some efficacy in patients with aggressive forms of RR-MS who are not responding to IFN-βs or glatiramer acetate; physicians interviewed estimate that this subpopulation represents up to 10% of RR-MS patients. However, physicians' concerns about the drug's safety have limited its use. Physicians report that mitoxantrone's cardiotoxicity requires cardiac, blood count, and liver monitoring. In addition, the risk of opportunistic infection and the associated risk of developing secondary AML prevent its more frequent use. The occurrence of secondary AML in MS patients has diminished mitoxantrone's differentiation from natalizumab, to the point that neurologists will not have a clear choice of first-line therapy drug to treat aggressive forms of RR-MS until emerging therapies launch, starting in 2010.

Mycophenolate Mofetil

MMF is an immunosuppressant approved for transplant rejection. It was initially launched in 1995 in the United States for this indication and is available in both Europe and Japan (see Table 4-14). In 2003, Aspreva Pharmaceuticals obtained worldwide rights to MMF, except for Japan, where MMF was licensed to Chugai Pharmaceuticals; Chugai was acquired by

Table 4-14

Key Facts: Mycophenolate Mofetil
Mycophenolate Mofetil
Launch Date: 1995 (US); 1998 (EU), 1999 (JA) for transplant rejection.
Brand Name and Marketer: Roche/Aspreva's CellCept/Munoloc.
Decision Resources' Expected Generic Entry: 2009 (US); 2011 (FR, GE, IT); 2007 (SP); 2010 (UK); 2012 (JA).
Formulation and Dose: 1 g (oral) twice daily.
Mechanism of Action: Mycophenolate mofetil is an immunosuppressant. It inhibits T-cell proliferation and potentially interferes with leukocyte infiltration and recruitment to inflammatory sites.
Side Effects: Increased risk of opportunistic infections, diarrhea, decreased white blood cell count, sepsis, vomiting.
Development Activity: Two Phase II/III clinical trials are currently examining the safety and efficacy of mycophenolate mofetil in combination with Avonex in MS patients. Results are expected in 2007-2008.
Differentiating Features: Mycophenolate mofetil is not currently indicated for MS, although clinical trials in MS are under way. The drug's oral formulation is convenient for patients who do not want to self-inject, but the drug's broad immunosuppressive properties will prevent it from becoming a first-line MS therapy.
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Roche in 2002. Although not approved for MS, it is used off-label in a small percentage of patients with progressive forms of MS, primarily in the United States and France.

Although used off-label, MMF is in clinical trials to determine its efficacy in MS. A retrospective study examined 79 MS patients who had taken MMF (Frohman EM, 2004). The patients represented all MS subpopulations (14 patients with RR-MS, 61 with SP-MS, and 4 with PP-MS). Most patients were prescribed MMF as an adjunct to IFN-β or glatiramer acetate therapy; 15 patients who could not tolerate IFN-β or glatiramer acetate received MMF monotherapy. MMF was well tolerated by most patients. No definitive effect on disease progression was noted, but this study was uncontrolled, with a small (and varied) patient population. Further randomized, controlled studies are required to determine MMF's effect on disease progression.

An ongoing, small-scale Phase II/III clinical trial is examining the efficacy of MMF in combination with Avonex in early-stage MS patients. The primary end point for this one-year, randomized, placebo-controlled study is the safety and tolerability of the MMF/Avonex combination. Disease progression (as measured by EDSS and ambulation index) and rate and number of relapses (as assessed by MRI) are secondary end points. This study is expected to run through early 2007. It remains unclear whether early-stage MS patients will be willing to use an immunosuppressant combination (with its less favorable side-effect profile) early in the course of the disease when the symptoms of the disease are less pronounced.

The MMF and Avonex treatment combination is also being studied in RR-MS. A Phase II/III randomized, open-label, multicenter study will examine the safety and tolerability of the MMF/Avonex combination (as assessed by MRI changes). It will also investigate the effect of this drug treatment on relapse number and rate and disability progression. The study is recruiting patients and is slated to run through mid 2008.

MMF's oral formulation provides convenience despite daily dosing. As with all immunosuppressants, MMF carries a poor side-effect profile, including an increased risk of opportunistic infections. Because of these adverse effects, MMF will not become a first-line therapy for MS even if it receives regulatory approval for this indication.

Treatment Trends

Overview

Diagnosis and Referral

Diagnosing MS is difficult, largely because of the variable and transient course of MS symptoms, the similarity of some symptoms to symptoms of other neurological or inflammatory disorders, and the lack of a conclusive diagnostic test. Because of this complexity, primary care physicians (PCPs) and general practitioners (GPs) refer patients to neurologists for a definitive diagnosis in each of the seven major pharmaceutical markets that we cover (United States, France, Germany, Italy, Spain, United Kingdom, and Japan). Following their diagnosis, neurologists initiate and supervise drug treatment.

Ideally, physicians base their MS diagnosis on evidence of neurological deficits resulting from damage to at least two areas of CNS white matter, as assessed by MRI. To meet requirements of a diagnosis of MS, symptoms must persist for more than 24 hours, and separate episodes must occur at least one month apart. Patient medieal history, including the date of symptom onset, the rate of progression or resolution of symptoms, and the duration of remissions, is important in the diagnosis of MS and is supported by the results of a neurological examination. Physicians also consider risk factors such as female gender, age between 20 and 35, birthplace within northern latitudes, and positive family history.

Criteria have been established to facilitate correct diagnosis, and modifications to these criteria have periodically been made to reflect the increased understanding of MS. In 2001, the International Panel on the Diagnosis of MS issued modified MS diagnostie criteria (McDonald WI, 2001) that were intended to supersede the diagnostic criteria published by C.M. Poser and colleagues in 1983 (Poser CM, 1983). Most physicians prefer the categories in the new criteria because they facilitate diagnosis of MS in patients with a variety of presentations, ineluding monosymptomatic demyelinating disease suggestive of MS (early-stage MS or CIS), RR-MS, SP-MS, and PP-MS. In 2005, the McDonald criteria were revised to simplify and accelerate diagnosis (Polman CH, 2005). In most of the major pharmaceutical markets that we cover, physicians are gradually adopting the McDonald criteria, although some physicians continue to diagnose MS according to the more-familiar Poser criteria. Many Japanese physicians use neither the Poser nor the McDonald criteria; instead, guidelines published by the Ministry of Health, Labor, and Welfare (MHLW) serve as the primary diagnostic tool for MS, according to physicians interviewed.

Unless the mcdical history and physical examination are unusually suggestive of MS, a definitive diagnosis requires additional diagnostie tests. These tests, used in each of the major markcts that we cover, include the following:

- *Magnetic resonance imaging.* MRI of the brain, spinal cord, and optic nerves is used to exclude other pathologies, visualize lesions, and detect various aspects of the disease process. Although MRI is the most sensitive tool for detecting brain lesions in MS patients, it is not MS-specific. In an attempt to minimize the occurrence of false-positives, the International Panel on the Diagnosis of MS issued a list of stringent criteria that should be satisfied before basing a diagnosis of MS on MRI findings; these imaging criteria were updated and clarified in 2005 (McDonald WI, 2001; Polman CH, 2005). The AAN published guidelines in 2003 (reaffirmed again in October 2005) that support use of the McDonald criteria in diagnosing MS (Frohman EM, 2003). The McDonald criteria incorporate advanced MRI imaging technologies, including detection of T2-weighted lesions and Gd-enhancing lesions, which increase sensitivity and specificity compared with previous methods. Lack of access to MRI can impede the diagnostic process in some European countries; thought leaders say dclays in diagnosis are most common in rural areas.

- *Evoked potential studies.* These studies consist of a battery of electrophysiological tests that measure the time it takes an electrical signal to travel across visual, auditory, or somatosensory nerves to the brain. Delayed signal transduction indicates impaired nerve conduction, a sign of MS. Like MRI, evoked potential studies may be useful in demonstrating clinically silent lesions, especially lesions in the visual, auditory, somatosensory, or central motor pathways. However, the changes detected by evoked potential evaluations are not specific to MS and may signal many other CNS diseases. For this reason, evoked potential studies are generally conducted after MRI and clinical examination, often to confirm the presence of a second lesion.
- *Cerebrospinal fluid (CSF) analysis.* This type of analysis is used to verify an MS diagnosis. Breakdown products of myelin may be present in the CSF of MS patients. Elevated levels of immunoglobulin G (IgG) antibodies (e.g., IgG levels greater than 12% of total CSF protein) in the CSF support a diagnosis of MS. The presence of oligoclonal bands of IgG on electrophoresis of CSF is useful in assisting with diagnosis, but it is not specifie to MS. A positive CSF finding is no longer required to diagnose PP-MS (Polman CH, 2005).

Although experts interviewed state that MRI outcomes are most commonly used to aid in the diagnosis of MS, they acknowledge that relying solely on MRI is insufficient. As one expert states, "Diagnosis of multiple sclerosis still remains clinical with much help from MRI and other tests, including CSF analysis, and from visually evoked responses, but the diagnosis essentially remains clinical." Experts also acknowledge that MRI has limitations in MS diagnosis. According to one neurologist, "An important challenge is to diagnose the disease when MRI is negative. In 10% of cases, it is a very important question. Another issue is to detect lesions that are clinically silent, when lesions of the white matter are not demonstrated by MRI but can be there."

During treatment, physicians evaluate patient response to prescribed therapies. The EDSS is a standard measurement of clinical efficacy in studies of investigational drugs and is often used in practice to evaluate MS patients' level of disability. The EDSS measures disability in half-step increments, beginning with 0 (normal) and ending with 10 (death due to MS). The EDSS score is based on a two-part assessment. First, the physician evaluates the level of impairment in the eight functional systems (FS): pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral, and other. Each system is assigned a grade ranging from 0 (normal function) to 6 (total loss of function). Second, the physician assesses the patient's ability to walk without assistance for an ambulatory disability score of 1-10. The FS grade and disability score together determine the overall EDSS score. Generally, patients with an EDSS score higher than 3.5 are presumed to have a rapidly advancing course of the disease and a poor prognosis, although a precise prognosis of MS is notoriously difficult to determine.

Increasingly, neurologists are diagnosing MS earlier in the disease progression, and experts interviewed predict that this practice will eventually be broadly accepted, in part because patients want earlier diagnosis and

treatment (Janssens AC, 2004). In addition, neurologists are increasingly aware of the benefits of beginning treatment early in the disease. As one neurologist states, "The earlier you diagnose and treat, the quicker you're going to be able to begin therapy and make a difference, and, obviously, the earlier you stop the disease, the better the outcome is likely to be." However, according to neurologists interviewed, current diagnostic tests are not specific for MS, so they may not produce definitive results in early-stage MS patients. Genetic markers of MS may aid in diagnosis, and the genes most consistently implicated in genetic risk of MS are the major histocompatibility complex (MHC) class II alleles (also called human leukocyte antigen [HLA] alleles) HLA-DR2 and HLA-DR4 (Noseworthy JH, 2000). However, although this genetic background is present in 50-75% of MS patients (Oksenberg JR, 2005a), the absence of HLA-DR2 and HLA-DR4 in 25-50% of the MS population suggests that these genes will not reliably identify all MS patients; additional genetic markers still need to be identified (see Chapter 5, "Development Hurdles and Treatment Challenges," and Chapter 9, "Market Outlook").

CIS represents isolated demyelinating events that may be followed by remission for several years; experts interviewed note that 20-30% of CIS sufferers remain relapse-free five years after an event. More CIS patients are likely to be identified, neurologists interviewed report, as the availability of MRI continues to spread, physicians become more familiar with the McDonald criteria, and patient awareness strengthens. Most of the physicians interviewed continue to demand a more specific diagnostic test for establishing clinically definite MS. The presence of antibodies against myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) in the CSF of MS patients is an emerging prognostic marker that may lead to earlier detection of MS (Berger T, 2003), but the reliability of MOG and MBP as a predictor of MS is unproven (Lampasona V, 2004; Reder AT, 2004).

The length of time between clinical onset and a diagnosis of MS is estimated to be one to four years, although data show that the lag is shortening, owing to greater disease awareness and improved specialist care (Dahl OP, 2004; Esbjerg S, 1999; Grimaldi LM, 2001; Nicoletti A, 2001; Pina MA, 1998; Pugliatti M, 2001; Sadovnick AD, 1993).

Treatment Guidelines

International guidelines, published in 2002 by the AAN and the MS Council for Clinical Practice Guidelines, evaluate the clinical utility of available disease-modifying therapies and make recommendations for treating MS (Goodin DS, 2002). Reaffirmed in October 2003, these international guidelines form the basis for individual country guidelines, which exist in each of the markets that we cover. In general, thought leaders interviewed say, physicians follow these national protocols when prescribing drug therapy for MS.

Pharmacological Treatment

MS therapy comprises separate treatments for symptoms, acute exacerbations, and disease progression. This report focuses on therapies that are used to ameliorate relapses and slow disease progression. The upcoming

region-specific sections highlight variations in the way these agents are used in the major markets under study.

In all the major markets under study, short-term, high-dose corticosteroid treatment for acute relapses is standard (e.g., methylprednisolone, prednisone). IFN-β therapy—including IFN-β-1a (Avonex or Rebif) and IFN-β-1b (Betaseron)—or glatiramer acetate therapy is first-line treatment for patients with RR-MS; in some European markets, glatiramer acetate is viewed as a second-line rather than a first-line therapy, although this practice is changing as physicians become more familiar with the drug. In the United States and some European markets (e.g., Germany), physicians are also using natalizumab, although it has been relegated to second- or third-line therapy because of wariness over the drug's safety risks.

Prescribing patterns for the disease-modifying drugs vary among and within markets, depending on drug availability and physician/patient preference. When choosing among the available disease-modifying agents, physicians often consult closely with patients; the choice of therapy is generally based on the form of the disease, disease progression, and the patient's preference for method of administration and tolerance of side effects. Most MS patients are highly educated in their disease and have considerable control over therapy decisions, according to experts interviewed.

Controversy exists within the MS community about whether to treat a patient upon a diagnosis of early-stage MS or whether treatment should be initiated only after a second relapse. Patients and physicians are reluctant to begin self-administered injections in the event the disease follows a benign course. In addition, in some markets, restrictions imposed by third-party payers or regulatory agencies prevent the use of expensive MS drugs in specific subsets of RR-MS patients (e.g., patients who have early disease or low EDSS scores). Nevertheless, this patient population represents an opportunity for drug developers to expand their drug-treated population. Avonex has been approved for early-stage MS in the United States and Europe since 2002. Betaseron received expanded labeling for early-stage MS in Europe in May 2006 and in the United States in October 2006. In July 2006, Rebif's labeling was expanded in Europe to include early-stage MS.

Treatment options for patients with CP-MS are sorely lacking; in most markets, these patients are usually treated only with symptomatic therapy. The exceptions are the use of Betaseron and Rebif for SP-MS patients who are relapsing and some off-label prescription of Avonex and, to a lesser extent, glatiramer acetate, for patients with SP-MS. Cytotoxic and immunosuppressant therapy is used to treat patients with CP-MS, but use of these agents varies among markets. The agents used include mitoxantrone (approved for SP-MS in the United States) and often off-label use of mycophenolate mofetil, methotrexate, cyclophosphamide, and azathioprine.

Combination therapy is not widely used in any of the major markets, with the exception of concurrent corticosteroid treatment for acute attacks. Patients who are candidates for polytherapy are those patients who continue to deteriorate despite treatment with disease-modifying therapy. Studies

continue to investigate the therapeutic benefits of combination therapy for treating MS (Giacomo L, 2004).

Specific information on patient share and pricing is detailed in Appendix B, "Market Forecast Methodology."

Economic Issues

Across the major markets, thought leaders interviewed state that, despite the high price of MS therapies, cost typically does not play a significant role in treatment decisions. In certain situations, however, some patients have difficulty obtaining coverage for treatment. Most European countries set restrictions on the types of patients who can receive MS therapies to control use and cost; however, physicians interviewed say that these restrictions have not prevented patients who may benefit from drug treatment from getting the drugs they need. Historically, the United Kingdom has been the only country in Europe to prohibit access to disease-modifying MS drugs, but in 2002, the Department of Health introduced a risk-sharing scheme that is slowly making MS drugs more accessible to patients. Under this novel plan, pharmaceutical companies reimburse the government for disease-modifying therapy if patients do not improve during drug treatment. In Japan, the MHLW covers the cost of MS drugs with a small copayment.

Major-Market Profiles

United States

In the United States, neurologists diagnose and treat the vast majority of MS patients. Many patients are referred to a neurologist by a PCP who has already made a tentative diagnosis. Most neurologists favor the McDonald diagnostic criteria because they integrate MRI with the standard procedures that include medical history and neurological examination. Thought leaders believe that undertreatment of MS is still widespread among patients cared for by PCPs and neurologists who do not specialize in MS because of PCPs and general neurologists' unfamiliarity with the benefit of drug treatment.

According to experts interviewed, an increasing number of neurologists are diagnosing patients after a single demyelinating event (i.e., CIS), but others remain unconvinced that a diagnosis of MS can be made at this point in the disease progression and so wait until two clinical events have occurred. One U.S. neurologist explains, "I lean toward starting treatment early if there is an extremely high risk. In situations where I'm not so sure whether the patient has MS, I think it makes most sense to wait rather than commit them to treatment." Guidelines published by the National Multiple Sclerosis Society (NMSS) recommend that disease-modifying therapy commence as soon as possible after clinical diagnosis is confirmed (National Multiple Sclerosis Society, 2003) and that therapy be continued indefinitely unless patients experience intolerable side effects or demonstrate no benefit from drug therapy. Experts interviewed estimate that approximately 60% of diagnosed MS patients in the United States receive disease-modifying drugs.

All five disease-modifying therapies (Betaseron, Avonex, Rebif, glatiramer acetate, and natalizumab) are prescribed for patients with RR-MS. Of the three IFN-β drugs, Avonex has the largest patient share (estimated at 43%)

because of its popularity with patients who are unable or unwilling to inject themselves frequently. However, experts interviewed increasingly choose Rebif (patient share 15%), which was launched in 2002, and continue to prescribe Betaseron (patient share 18%) because these therapies' higher doses and more-frequent administration are perceived to be more efficacious based on results from the EVIDENCE trial (discussed earlier in this chapter), particularly in patients with more active disease.

Glatiramer acetate is increasingly being prescribed as first-line therapy in RR-MS, especially for patients with early and/or mild disease, based on the drug's superior tolerability over that of IFN-β therapy. Glatiramer acetate, which we estimate was prescribed to 33% of RR-MS patients in 2005, is also prescribed for patients who fail to respond to IFN-β treatment.

Natalizumab uptake has been modest in the United States since its relaunch in July 2006. The risk of developing PML, combined with physician wariness and the stringent requirements put forth to monitor the drug's safety and administration, has hindered its uptake. In addition, the implementation of the TOUCH Prescribing Program and negotiations with third-party payers for reimbursement of the drug have slowed natalizumab's uptake. Physicians are prescribing natalizumab to patients who do not respond to the IFN-βs or glatiramer acetate and to patients with aggressive RR-MS.

For patients with worsening RR-MS (defined as a stepwise progression of disability between relapses), physicians may prescribe mitoxantrone, the only chemotherapeutic agent approved for aggressive RR-MS and SP-MS in the United States. In May 2005, because of the drug's modest efficacy and poor side-effect profile associated with long-term use, the FDA added a black box warning to the drug's U.S. label recommending that use of mitoxantrone be carefully supervised (Goodin DS, 2003). Many physicians are leery about administering mitoxantrone to RR-MS patients; physicians interviewed who do administer the agent are careful to limit the course of treatment to two years, in accordance with the FDA-imposed lifetime dose limit of 140 mg/m^2 (Ghalie RG, 2002). Other chemotherapeutic agents are sometimes prescribed off-label, including mycophenolate mofeil, methotrexate, and azathioprine, to RR-MS patients who cannot tolerate or do not respond to IFN-β and glatiramer acetate and to those patients who refuse injectables.

In 2003, Betaseron became the first disease-modifying agent approved for treating SP-MS with relapses in the United States; physicians also prescribe Rebif and Avonex off-label for this subtype. Chemotherapeutic agents are considered second-line therapies for patients with SP-MS. Combination therapy consisting of a chemotherapeutic agent and IFN-β are given to a small percentage of patients with aggressive SP-MS who do not respond well to IFN-β treatment alone. Corticosteroids are used to treat acute exacerbations at all stages of MS.

Treatment of PP-MS with IFN-β or glatiramer acetate is minimal because these drugs have not proved to be efficacious in this subtype; chemotherapeutics are more common therapies for patients with PP-MS (though they are rarely used because of lack of efficacy).

Experts interviewed by Decision Resourees state that, in general, cost is not an issue that affeets treatnent deeisions. However, third-party payers' reluctance to reimburse expensive therapies, except in the treatment of very specifie patient groups (e.g., younger patients, patients with moderate disability), ean be an obstaele to treatnent. Health care providers increasingly ineentivize the use of generics in lieu of branded products to control eosts, but no generic forns of current therapies are available. Prineipal disease-modifying therapies are biologie agents, and regulatory frameworks have yet to be established to allow entry of biogeneric drugs into the U.S. market. Patients who lack health eare coverage or have high copayments may go without recommended drugs because they cannot afford them. Nevertheless, many of these patients are able to obtain MS drugs through patient support programs sponsored by pharmaceutical companies. Physicians interviewed claim that a very small percentage of MS patients are not being treated owing to financial reasons.

Elderly MS patients face particular obstaeles in paying for MS treatment. The new Medicare Prescription Drug Benefit program (Medicare Part D) provides prescription drug coverage to Medicare beneficiaries for the first time. Guidelines have been established by the United States Pharmacopeia (USP) for prescription drug plan (PDP) formularies recommending that participating plans cover two therapies from every therapeutic category and class. However, IFN-β therapies fall within a broader pharmacological class (immunomodulators) that also includes IFN-α, IFN-γ, and other agents; thus, the requirement to cover a minimum of two therapies could restrict reimbursement of MS therapies. Beginning in 2007, the USP guidelines will recognize four distinct Formulary Key Drug Types (FKDTs) within the broad classes, including the IFN-βs. Plans will be required to cover at least one agent in each FKDT. This change in Medicare formulary guidelines is unlikely to have a major impact on coverage of MS therapies; MS therapies received adequate coverage under the previous guidelines, and that coverage is not expected to change.

The comprehensiveness, savings, and/or restrictions of drugs covered on each PDP formulary vary substantially among PDPs in the United States based on each agent's plan-specific tier placement (which determines the level of cost-sharing), quantity limitations, or required prior authorization (Hoadley J, 2006). Analysis of the formularies of ten national PDPs reveals that the principal MS therapies (the disease-modifying agents) are frequently considered "specialty products," a high-level tier for expensive biotechnology or injectable products that often bear higher copayments, prior authorization, and quantity limitations. As mentioned, because of ongoing negotiations, few PDPs cover the cost of natalizumab. Although most Medicare PDPs encourage the use of generics, there is no opportunity for MS patients to substitute less-expensive generics for these expensive MS therapies. In addition, because of formulary restrictions or financial incentives, elderly MS patients taking a carefully balanced regimen of particular products may be forced to switch products.

Restrictions on drug coverage may complicate benefits owed to elderly MS patients. There is a wide variation among the benefits offered on each of the 1,429 PDPs available, in addition to elderly patients' likely confusion and/or

wariness of the program, limitations in drug coverage offered by participating plans, and the risk of a sizable "coverage gap." This gap (colloquially known as the doughnut-hole, during which time beneficiaries are 100% responsible for their drug costs) could substantially increase the out-of-pocket expenses of Medicare beneficiaries with heavy prescription drug use or expensive medications (both of which are likely to apply to MS patients). Importantly, low-income beneficiaries will be eligible to receive subsidies that will eliminate most out-of-pocket costs, and many plans will offer significant cost-savings to full-benefit enrollees, including reduction or elimination of deductibles, premiums, or the doughnut hole.

Although the full impact of Medicare Part D on the treatment of MS remains unclear, overall, we do not predict that any newfound cost-savings will become significant market drivers for MS therapy in the United States. Likewise, although cost often compels seniors to cut medications (Safran DG, 2005), we do not anticipate reductions in compliance to vital MS therapies to lower out-of-pocket costs. However, we expect Avonex to lose its previous reimbursement advantage (because of its in-office IM administration) over the subcutaneously delivered drugs and some financially underprivileged patients to lose their free coverage of the expensive disease-modifying agents with the end of patient assistance programs. (For more information, see the following reports: Progress report on the Medicare Prescription Drug Benefit. Decision Resources, Inc. *Spectrum, Pharmacoeconomics, Pricing, and Reimbursement.* Issue 18, 2005; Opportunities and challenges in emerging U.S. geriatric drug markets. Decision Resources, Inc. *Spectrum, Therapy Markets and Emerging Technologies.* Issue 10, 2005.)

Europe

In each of the European markets we cover (France, Germany, Italy, Spain, and the United Kingdom), most patients are referred by GPs to neurologists for diagnosis of MS. France has more neurologists per capita than other markets under study (Sicart D, 2005), and Spain has the greatest number of neurologists who specialize in MS. The United Kingdom has the fewest neurologists per capita (NHS Modernisation Agency, 2005) and, consequently, fewer neurologists who specialize in MS. The majority of neurologists in Germany and Italy now use the new McDonald diagnostic criteria instead of the Poser criteria to diagnose MS. Both the McDonald and the Poser criteria are used in France and Spain to diagnose MS, although more neurologists are starting to use the McDonald criteria. In the United Kingdom, most neurologists use the Poser criteria to diagnose patients, but use of the McDonald criteria is slowly increasing as physicians become more familiar with them.

In all markets, with the exception of the United Kingdom, physicians are starting to diagnose early-stage MS more frequently than in the past, in part because of the increasing availability of MRI and the new diagnostic criteria, although experts interviewed in Germany state that some physicians are still not comfortable making a diagnosis after a single demyelinating event. However, German experts note that recommendations for diagnosis have changed in recent years in favor of early diagnosis. Asserts one German

neurologist, "We had recommendations that started eight years ago that any patients who have two or more relapses within a year should be treated, and then we had recommendations that it should be two relapses within the last two years. Then, we were told to treat earlier. Now we are quite likely to treat MS patients not after a couple of relapses but with, on average, 1.38 relapses." In contrast, in the United Kingdom in accordance with NICE guidance, physicians do not prescribe disease-modifying therapies after a single demyelinating event; they wait until after a second relapse.

Specialized MS centers are used in all five markets. GPs often refer patients to neurologists at these centers. Diagnosis of MS, including early-stage MS, occurs primarily at these centers, where there is a routine use of MRI use and familiarity with new diagnostic and treatment protocols. However, the role of these centers differs between countries. In Germany, some neurologists who are not affiliated with such centers (but who may consult with MS specialists in those centers) still diagnose and treat patients, while in Italy, only those physicians affiliated with certified MS centers are allowed to initiate and supervise MS treatment. Once diagnosed, patients typically continue treatment under the care of neurologists at these centers. European physicians note that they encourage MS patients to play a significant role in choosing therapy because this practice is associated with improved patient compliance with therapy, but others note that patients expect treatment decisions to be made by the physician. The percentage of patients receiving disease-modifying drugs differs among markets; few patients are treated in the United Kingdom, while as many as 70% of Spanish patients receive treatment in large, specialized MS centers.

National guidelines for treating MS have been established in each country. In France, Germany, Italy, and the United Kingdom, the guidelines stipulate that physicians can prescribe disease-modifying therapy to patients who have had at least two attacks in the previous two years. In Spain, differences in local protocols cause treatment to vary slightly from region to region, despite the existence of national guidelines.

IFN-β therapy is universally considered first-line therapy in all five markets, although which IFN-β has the largest patient share varies in each market. Avonex is the most frequently prescribed IFN-β agent in France, although use of Rebif is increasing in this country. Avonex is typically used for early treatment of MS before patients are switched to Betaseron or Rebif, which are prescribed more or less equally. Italian physicians typically prescribe Rebif or Avonex over Betaseron, which is generally reserved for patients with more-progressive disease. In contrast, the three IFN-β therapies are prescribed more or less equally in Spain and Germany for RR-MS, while U.K. physicians prescribe Rebif most often.

Glatiramer acetate is considered either a first- or second-line therapy, depending on the market. The drug is prescribed as a first-line therapy in Germany (estimated patient share 20%) and Spain, although it is not widely used in Spain and so has only 9% of the patient share in that market. In Italy, it is considered a second-line therapy and is used for patients who do not respond to or cannot tolerate IFN-β drugs. However, in Italy, as well as in France and the United Kingdom, patient share of glatiramer acetate is

steadily increasing, and we expect this increase to continue through 2010. Indeed, in the United Kingdom, where glatiramer acetate recently launched, it has an estimated patient share of 12%, compared with Rebif's patient share of 8%. We expect that during the second half of the forecast period, glatiramer acetate's patient share will decline in these markets as emerging agents launch.

Natalizumab use has been limited to Germany since its European launch in July 2006. It is available in several European countries but, of the five European markets we cover, only in Germany and the United Kingdom. The drug is being launched in additional countries through 2007. Among the countries in which it is currently available, uptake has varied; the majority of patients are in Germany. Physicians are wary of natalizumab's side effects, and many are withholding from widely prescribing the drug until the risk of side effects is better determined.

Rebif and Betaseron are approved for SP-MS with and without relapses in all five markets, but Betaseron is preferred for this indication in Italy. Avonex is sometimes used off-label in this patient population in Germany and Spain. Chemotherapeutic agents are also prescribed for SP-MS, particularly in severe cases of SP-MS or when other drugs fail to produce a response. Mitoxantrone is the agent most commonly used for SP-MS; additional chemotherapeutic agents, including azathioprine, cyclophosphamide, and, particularly in France, mycophenolate mofetil, are prescribed only if other therapies prove ineffective.

In all markets, chemotherapeutic agents are often prescribed for PP-MS, although the agent of choice varies in each market. Corticosteroids are used in all five markets to treat acute exacerbations of MS.

In all markets except the United Kingdom, MS treatments are reimbursed by the national health care system of the respective country. Patients in France and Germany are required to pay modest copayments, although in France, private insurance options provide supplemental coverage that eliminates out-of-pocket expenses. Off-label use is not reimbursed, and, at least in Italy, disease-modifying agents are not reimbursed when prescribed for early-stage MS. In Spain, outpatient drugs for chronic diseases such as MS are reimbursed at 90% by the Sistema Nacional de Salud (SNS; National Health System); inpatient medications are reimbursed 100%. Because the SNS assumes 100% of drug costs for retirees, pensioners, disabled citizens, and invalids, MS patients generally receive their medication for little or no charge.

Physicians in England and Wales abide by the national ruling issued by NICE. In February 2002, NICE did not find the use of IFN-β therapy and glatiramer acetate efficacious in the treatment of MS, determined these therapies were not cost-effective, and decided that they should not be reimbursed by the United Kingdom's National Health Service (NHS) in those countries. This development, in turn, led NHS to restrict the use of disease-modifying drugs, impose tight budgetary controls on hospitals, and drive most patients to pay out-of-pocket for therapy. NICE's evaluation of these

drugs has caused them to be negatively perceived as marginally effective with no significant impact on disability, and thus they are not widely used.

As an alternative for reimbursement, NHS announced a new prescription plus monitoring (or risk-sharing) scheme under which the NHS and participating pharmaceutical companies share the financial risk associated with disease-modifying MS therapy in England and Wales. Implemented in May 2002, the risk-sharing scheme specifies that the NHS will cover the cost of therapy for patients in England and Wales who meet specific criteria defined by the Association of British Neurologists (ABN). Physicians are allowed to prescribe any of the available disease-modifying therapies (Avonex, Rebif, Betaseron, or glatiramer acetate) for patients who fulfill the ABN criteria. MS patients will be assessed annually during disease-modifying treatment for ten years in a monitoring study using the EDSS; if a drug does not satisfy certain efficacy criteria, the relevant pharmaceutical company must repay a certain percentage of the drug's price to the government, based on efficacy achieved, to maintain its cost-effectiveness to the NHS. Overall, the introduction of the risk-sharing scheme in the United Kingdom has allowed more MS patients to receive disease-modifying therapies, although insufficient financial resources, a limited number of neurologists and nurses, poor coordination of the risk-sharing scheme, and differing access to these therapies because of uneven Primary Care Trust funding remain obstacles to therapy (Hawkes N, 2006). (For more information on pricing and reimbursement issues, see the following reports: The pricing and reimbursement environment for biologics. Decision Resources, Inc. *Spectrum, Pharmacoeconomics, Pricing, and Reimbursement.* Issue 12, 2003; NICE's impact on the U.K. pharmaceutical market. Decision Resources, Inc. *Spectrum, Pharmacoeconomics, Pricing, and Reimbursement.* Issue 12, 2004; Pharmaceutical pricing, reimbursement, and prescribing in Germany. Decision Resources, Inc. *Spectrum, Pharmacoeconomics, Pricing, and Reimbursement.* Issue 17, 2004; Pricing and reimbursement issues in neurology. Decision Resources, Inc. *Spectrum, Pharmacoeconomics, Pricing, and Reimbursement.* Issue 9, 2006.)

Japan

In Japan, GPs rarely play a role in diagnosis and treatment of MS because of their lack of knowledge and experience with MS. Instead, most patients present to neurologists directly for diagnosis; referrals are uncommon. Japanese neurologists and specialists do not use the McDonald or Poser diagnostic criteria but instead use criteria set forth by the MHLW (which includes diagnostic categories RR-MS, SP-MS, and PP-MS). Experts state that early diagnosis in Japan is not common, but recently, some physicians are prescribing disease-modifying therapies after a single demyelinating event. Following diagnosis, neurologists or specialists initiate and supervise treatment. Physicians are primarily responsible for deciding the course of treatment.

The Japanese Society of Neurological Therapeutics and the Japanese Society of Neuroimmunology have established treatment guidelines for MS. Physicians interviewed for this and past reports disagree about the utility of these guidelines: some thought leaders consider them useful in determining the appropriate course of treatment but are unsure how many neurologists

adhere to them closely; others state the guidelines merely present the treatment options and do not provide a useful treatment algorithm—treatment decisions are left up to the knowledge and expertise of the prescribing neurologist. Experts interviewed state that there is usually a delay before treatment initiation, especially with mild or early-stage MS, owing to the difficulty of diagnosis and patient resistance to the burdensome therapies.

Betaseron had orphan-drug status in Japan and, until November 2006, was the only disease-modifying therapy available. According to physicians interviewed, the vast majority of drug-treated patients (76%) receive Betaseron treatment, primarily patients with RR-MS, and these patients generally receive treatment for two years or longer. Although Avonex launched in Japan in November 2006, physicians interviewed for this report do not believe that the drug will dominate the Japanese market because clinical trials suggest that higher-dose, more-frequent administration of an IFN-β is more effective in treating MS (Deisenhammer F, 2000; Durelli L, 2002). Few other therapies are available in Japan because the low prevalence of MS in this market generates little incentive for launching new drugs.

Japanese specialists rarely prescribe standard immunosuppressive therapy because they are wary of side effects. Mitoxantrone is not formally approved to treat MS in Japan, although physicians may prescribe mitoxantrone off-label for SP-MS patients who do not respond to Betaseron. Azathioprine and methotrexate are not approved for MS but may be prescribed for some patients who do not respond to or cannot tolerate Betaseron. Cyclophosphamide is rarely used because it is perceived to have toxic side effects.

As is the case in the other markets, corticosteroids are used in Japan to treat acute exacerbations of MS. There is no standard combination therapy in MS treatment in Japan.

Because MS is a government-certified disease, most of the costs of MS therapies are covered by the special public medical assistance program in Japan. The MHLW administers critical prescription reimbursement policies. In effect, Japan has universal health insurance, with coverage provided through employer programs and through community health programs for the unemployed, self-employed, and retired populations. Most Japanese citizens pay 30% of their medical costs, including drug expenses, depending on their income. MS outpatients generally pay a small monthly copayment, depending on the patient's financial status, totaling ¥11,500 ($105) per month, according to experts; MS inpatients typically pay higher copayments, up to ¥23,100 ($210) per month, again depending on their financial status. As of October 2003, patients who are certified as having severe MS can receive treatment at no cost. For elderly patients, the age threshold of eligibility for geriatric health care was set to gradually increase starting in 2002 from 70 to 75 years, with copayment set at either 10% or 20%, depending on income. However, like health care systems worldwide, Japan's system is moving toward a more cost-conscious approach and has proposed an increase in these copayments (Japan's government grapples with co-payments for the elderly, 2005). In the future, new MS drugs will need to satisfy standards of efficacy to qualify for reimbursement and demonstrate significant improvements over existing therapies to command premium pricing.

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Chapter 5

Development Hurdles and Treatment Challenges

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.5401.2615 ♦ Fax +81.3.5401.2617

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5. Development Hurdles and Treatment Challenges

Key Findings

- Drugs designed to reverse neuronal damage represent significant commercial opportunity in MS treatment. Most drugs in development target the autoimmune response, and little progress has been made in developing neuroprotective and remyelinating agents.
- The prevailing need for therapies that significantly delay disability progression will not be adequately addressed by drugs in development over the course of our 2005-2020 study period.
- Therapeutic options for patients with chronic-progressive MS (consisting of secondary progressive MS [SP-MS] and primary progressive MS [PP-MS]) remain limited. Only one therapy--BioMS Medical's altered peptide ligand MBP-8298--is in development specifically for SP-MS.
- Because current MS therapies are administered by injection or IV infusion, a drug with a more convenient oral formulation will be enthusiastically welcomed by physicians and patients and will improve patient compliance.
- Although five drugs in development have oral formulations and are expected to launch during our study period, their safety and efficacy profiles are not superior to those of current therapies. Safer, more efficacious agents are still needed.

"The greatest unmet need requires looking beyond anti-inflammatory drugs. Now we have probably a next phase in MS treatment, which will be the oral compounds. We do have more and more biologicals and antibodies to certain compounds, but they all tackle the inflammatory component. We definitely need something that concentrates on the degenerative component."

—Neurologist, Germany

Expert Commentary: Unmet Needs in Multiple Sclerosis

Unmet Need	Expert Opinion
Reversing neuronal damage	"What we really need are factors that can improve myelin survival and neuron axonal survival." — Neurologist, Italy "We are only targeting at present the inflammatory parts of the disease. We are not promoting remyelination or we are not trying neuroprotection, and most of the [current and emerging] drugs go on the inflammatory side of MS." —Neurologist, Spain
Preventing disease progression	"I think the most important effect would be trying to work toward preventing disability in patients. It's a very big challenge because people have been looking at MS treatments for over 20, 30 years and still we do not have something very good." — Neurologist, United Kingdom
Improved therapy for chronic-progressive MS	"It's the primary-progressive patients and the patients who have secondary progression who we can't really do much for, because the [current] treatments don't really have a real impact on the progressive phase of the disease." — Neurologist, United States
More convenient drug delivery	"I think there is a trend in developing new oral therapies, a lot of new trials are coming up, ongoing. It is hugely convenient from the patient's point of view and avoids unpleasantness of injections and injection-site reactions, so, yes, oral therapy will increasingly become more popular, or at least there will be a huge initiative to develop orally effective treatment for multiple sclerosis." — Neurologist, United Kingdom
Improved diagnostic criteria	"We need to establish a diagnosis very early in the disease, but with obvious data. Today, we use MRI and the MacDonald criteria to establish diagnosis in MS. It is necessary for all neurologists in the world, private neurologists or in hospitals, and so on to use these parameters, but the idea, the goal of that is to establish a diagnosis very early." — Neurologist, France "The problem still is recognizing the early symptoms, making the patients themselves or the general public aware of the early symptoms of MS and then getting the other specialties like the ophthalmologists, orthopedic surgeons, and even the GPs to acknowledge that certain symptoms need further neurological investigation because they may be an early symptom of MS." — Neurologist, Germany
Improved animal models	"What happens is that all the drugs are based on EAE [experimental autoimmune encephalomyelitis], and EAE is not representative of the disease in any way." — Neurologist, United States

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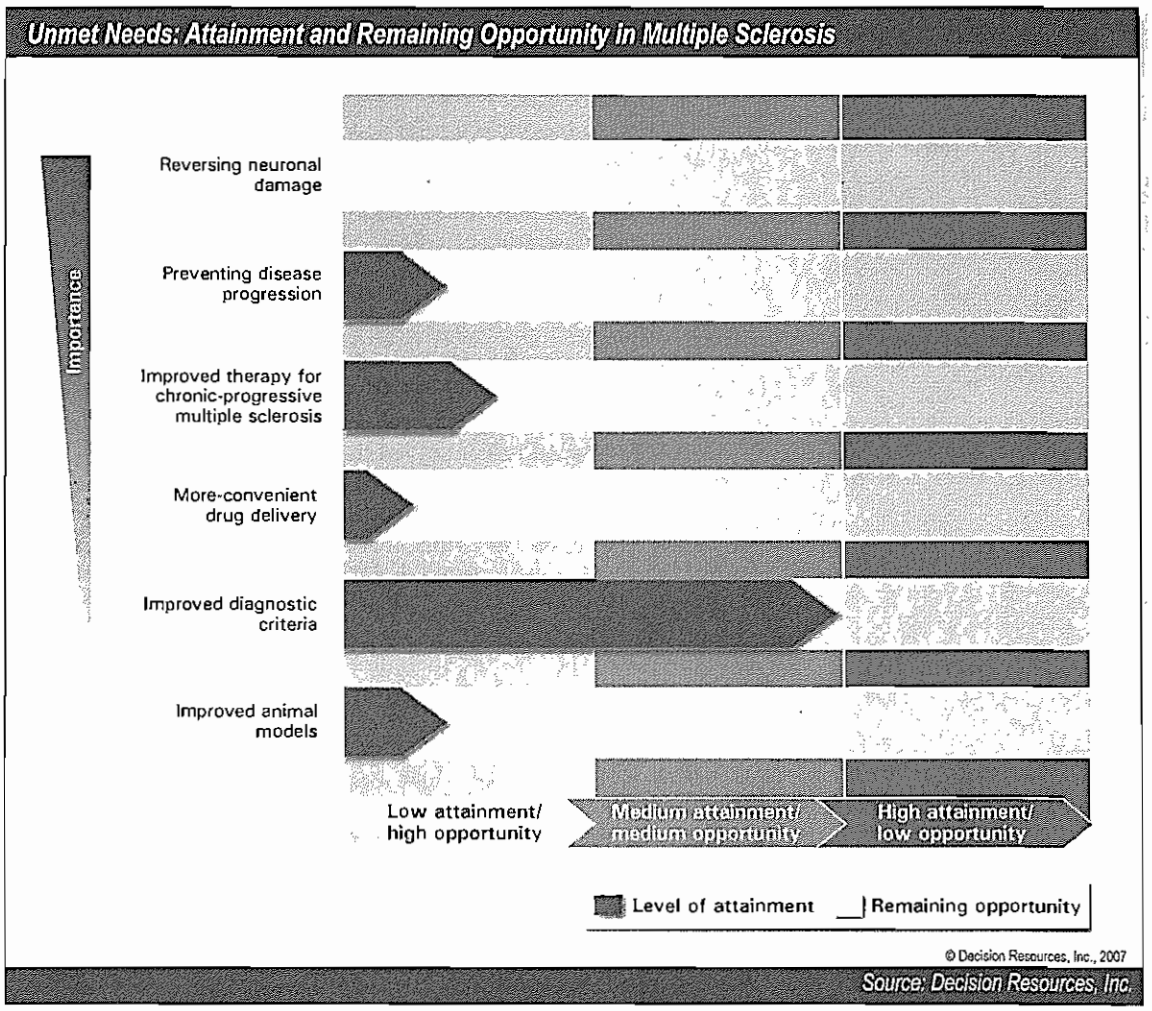
Evolution of Unmet Needs in Multiple Sclerosis

The introduction in the 1990s of the disease-modifying drugs—interferon-beta (IFN-β) therapies and glatiramer acetate (Teva Pharmaceuticals' Copaxone)—was a landmark improvement in multiple sclerosis (MS) therapy, but considerable unmet need remains. ("Disease-modifying" in this case refers to agents that affect the underlying cause of the disease rather than just ease symptoms of the disease, such as fatigue.) Although the relaunch of natalizumab (Biogen Idec/Elan's Tysabri) in the United States in 2006 provided MS patients with an additional therapeutic option, the significant safety risks associated with it will continue to restrict its use to patients with aggressive relapsing-remitting MS (RR-MS) who have failed other first-line therapies and are not immunosuppressed, despite its demonstrated improved efficacy over currently available therapies. We forecast that several

oral agents will launch beginning in 2010. Although these emerging agents (Merck Serono's cladribine [Mylinax], Novartis/Mitsubishi Pharma's FTY-720 [fingolimod], Sanofi-Aventis's teriflunomide, Biogen Idec's BG-12, and Teva/Active Biotech's laquinimod) offer improvements in convenience, experts anticipate that they will most likely be used third-line to currently available therapies as a result of their potential for severe side effects. One emerging agent in particular, BioMS Medical's MBP-8298, may offer a much needed therapeutic option for patients with CP-MS. Despite the efficacy of current and emerging therapies in delaying disease progression, no agent has demonstrated the ability to prevent the progression of MS.

Although emerging agents promise to reduce unmet need in MS patients, the urgent need for drugs to reverse demyelination and neuronal damage in MS will remain unfulfilled through the end of the study period. In addition, experts cite more-appropriate animal models and the streamlining of diagnostic criteria as unmet needs in MS. Figure 5-1 illustrates our ranking of the most important unmet needs in MS research and treatment.

Figure 5-1



Reversing Neuronal Damage

A critical need exists for therapies that can reverse neurological damage and the resultant disability caused by MS. Researchers indicate that axonal degeneration is a consistent consequence of demyelination and appears to occur early in the disease process (Trapp BD, 1998). Axonal degeneration is thus the likely pathological eorrelate of neurological impairment; therefore, experts interviewed say, the most effective restorative treatments for MS would repair injured axons as well as myelin. A U.S. neurologist states, "If we had an effective neuroprotective treatment, it would make a huge difference. We do have effective ways of suppressing inflammation, and if we can catch patients early enough, we can affect that, but the neuroprotective component, it's something that we are not doing that well."

Currently available disease-modifying drugs—IFN-β drugs, glatiramer acetate, and natalizumab—can reduce the number of exacerbations and delay lesion development, but none reverse disability or axonal damage. Experts interviewed by Decision Resources acknowledge this limitation of eurrent therapies, explaining that it is not clear, as one expert states, "how far these treatments are effective in reducing the rate of neural degeneration. None of these [current] treatments have proven to be effeetive in preventing neuronal loss or axonal degeneration, and although we are using these treatments, in the next 15 years, we will probably be combining newer drugs with a potential to reduce neuronal death and rate of progressive disability in multiple sclerosis."

Experts interviewed are cautiously optimistic that therapies that reverse the neurodegenerative effects of MS will be available in the next 15 years, although most experts admit that few companies are exploring such agents. However, as one expert states, "Moving away from always targeting the inflammatory response and beginning to target neurons and axons and glial cells, that's really the paradigm shift that has to occur with drug companies. Every drug company is targeting some other aspect of the immune response, and it seems to me if that were the case [that MS is solely an immune disease], we would have solved this disease a long time ago." Available trial data indicate that no drugs in late-stage development are likely to meet this need (see Chapter 8, "Emerging Neuroprotective and Remyelinating Therapies"), but some drugs in early-stage development may do so. Preclinical data from Eisai's E-2007, Acorda Therapeutics' recombinant human glial growth factor-2 (rhGGF2), and stem-cell therapy suggest that these therapies can repair axonal or myelin damage (Cannella B, 1998; Marchionni MA, 1999; Pluchino S, 2003; Smith T, 2002; Totoiu MO, 2004; Yamauchi T, 2002). Although experts interviewed believe that these therapies may offer some benefit, they do not expect them to repair all damage.

Experts interviewed state that when neuroprotective agents reach the market, they will likely be used in combination with disease-modifying therapies that target the immune response. With the exception of corticosteroid use in conjunction with IFN-βs or glatiramer acetate during acute flare-ups, neuroprotective and immunomodulatory drugs will be the only MS therapies used in combination because of concerns over severe side effects such as those that developed in patients taking both natalizumab and Avonex

(Biogen Idec's IFN-β-1a). Whether used in combination or as monotherapy, neuroprotective agents will address a vital unmet need in MS treatment.

Preventing Disease Progression

"We have no curative treatments. We can only delay disability progression, but nothing more. The efficacy is only mild or modest," states one Spanish expert, adding, "I need treatments with demonstrated efficacy on delaying--clearly delaying--or preventing disability, not only to reduce the number of bouts but to prevent--really prevent--disability." The need for therapies that prevent disease activity (specifically, the frequency of relapses and total lesion load made visible by magnetic resonance imaging [MRI]) and progression of MS (typically measured by patients' scores on the Kurtzke Expanded Disability Status Scale [EDSS]) is equally important, say experts interviewed. Although pivotal studies of all the disease-modifying drugs have demonstrated some efficacy in slowing disease activity, in terms of reduced annual exacerbation rates and MRI analysis of lesion load (Comi G, 2001; IFN-Beta Multiple Sclerosis Study Group, 1996; Jacobs LD, 1996; Johnson KP, 1995; Johnson KP, 2000; Paty DW, 1993; PRISMS Study Group, 1998; Simon JH, 1998), no treatments have been shown to completely eliminate new lesion formation or to halt disability progression. Natalizumab has demonstrated that it is the most effective agent in terms of preventing disease activity and progression; data from Phase III trials demonstrate that natalizumab reduces disability, disease progression, relapse rate, and lesions as assessed by MRI better than other currently available drugs. Although the drug's improved efficacy excited specialists worldwide, the risk of severe side effects and monitoring requirements, together with physician and patient wariness of the drug, has limited its use. We expect that, over the course of our study period, the drug will be prescribed to no more than 7% of RR-MS or SP-MS patients.

Most experts interviewed agree with the U.S. treatment guidelines, which state that disease-modifying agents probably slow sustained disability progression as measured by EDSS in the short term (less than five years) (Goodin DS, 2002). However, as one expert states, "So far, there are no treatments that can assure us of preventing disability accumulation over five or six years of therapy. This is really the greatest unmet need." Experts state that although current therapies represent progress in treating MS, additional therapies that are effective long-term (five to ten years) are still needed. "This is really an important objective because it is realistic to prevent disability at ten years of the disease, ten years after the introduction of the treatment," explains another expert. Experts stress that given the chronic nature of MS, efficacy in delaying and preventing disease progression is critical.

Improved Therapy for Chronic-Progressive Multiple Sclerosis

Physicians also call for improved therapy for patients suffering from CP-MS. Because current disease-modifying treatments target the inflammatory response, they are useful only in patients who continue to relapse, whose disease is suspected to be primarily inflammatory (RR-MS and relapsing SP-MS). We estimate that these patients represent 65% of the total diagnosed MS population, leaving the remaining 35% of patients, who have primarily

degenerative disease (nonrelapsing SP-MS and PP-MS), without adequate treatment options; this population is significant yet underserved. Few treatments are approved for SP-MS, no treatments are approved for PP-MS, and off-label treatment of these patients is rare, say experts interviewed. Approximately 15% of MS cases begin with PP-MS; 85% of MS patients begin with RR-MS, an estimated 50% of which will develop SP-MS within ten years, and 90% will eventually develop SP-MS (Keegan BM, 2002; Weinshenker BG, 1989). Because, as most experts agree, RR-MS is primarily an inflammatory stage of the disease and CP-MS is primarily a degenerative stage, drugs that are effective in CP-MS will likely have a different mechanism of action than drugs that effectively treat RR-MS.

Currently available disease-modifying therapies have not proved efficacious in CP-MS. "Primary-progressive patients feel very much disenfranchised because there's nothing for them. They've tried Avonex, they've tried beta interferon, they've tried that for primary progressive, and it's been very unconvincing, so we're very hopeful that there will be something for primary progressive people sooner rather than later," notes one expert. IFN-β drugs have demonstrated disappointing results when administered to patients suffering from SP-MS (Cohen JA, 2001; Goodkin DE, 2000; Li DK, 2001; SPECTRIMS Study Group, 2001), suggesting that IFN-β therapy is most effective in the minority of SP-MS patients whose disease still has inflammatory components and who continue to relapse. Despite their limited efficacy in CP-MS, IFN-β therapies are being approved for SP-MS patients. For example, IFN-β-1b (Bayer Schering Pharma's Betaferon/Berlex's Betaseron) is approved in Europe for all SP-MS patients and in the United States for SP-MS patients who relapse, and Rebif (Merck Serono/Pfizer's IFN-β-1a) is approved in Europe for relapsing SP-MS patients. According to experts interviewed, less than 40% of SP-MS patients continue to relapse, and the percentage of SP-MS patients who relapse declines over time. We estimate that this subgroup is 25-30% of the CP-MS population and only 10-12% of total diagnosed cases of MS. Some of the disease-modifying drugs on the market have been tested in patients suffering from PP-MS, but reported results have been disappointing (Leary SM, 2003; Montalban X, 2003).

CP-MS patients are also treated off-label with chemotherapeutics and immunosuppressants such as azathioprine (GlaxoSmithKline's Imuran, generics). These drugs fall short in efficacy, are associated with serious side effects, and require monitoring. Many physicians interviewed say that these factors restrict their use; indeed, many experts state that PP-MS patients receive only symptomatic treatment. We estimate that disease-modifying therapies, chemotherapeutics, and immunosuppressants are able to provide some treatment benefit to 25% of drug-treated CP-MS patients.

The SP-MS population that continues to relapse will benefit most from emerging therapies, including Merck Serono's oral cladribine and Sanofi-Aventis's teriflunomide, which are both being tested in the SP-MS population, as well as Novartis/Mitsubishi's FTY-720 (see Chapter 6, "Emerging Oral Immunomodulatory Therapies"). PDL BioPharma/Biogen Idec's MAb daclizumab (marketed by Roche as Zenapax for control of kidney transplant rejection) has demonstrated positive efficacy in SP-MS in Phase II trials, and we expect it to be used in up to 5% of CP-MS

patients, predominantly in the SP-MS population but with limited off-label use in PP-MS as well. One emerging drug, BioMS Medical's MBP-8298, has shown to be very effective in the subgroup of SP-MS patients who carry either the *HLA-DR2* or *HLA-DR4* gene. Although the number of MS patients with either of these genes is unknown, the percentage of patients carrying the *HLA-DR2* or *-DR4* gene may represent 50-75% of the total MS population, so the drug may be effective in 10-20% of the total MS population (Oksenberg JR, 2005). Only one agent, the MAb rituximab (Biogen Idec/Genentech's Rituxan), is being tested in PP-MS, but in the absence of efficacy and safety data, we are unable to forecast a launch for this agent in MS. Thus, although SP-MS patients, particularly those who continue to relapse, will have an increased number of therapeutic options, PP-MS patients will continue to have few therapeutic options throughout our forecast period.

More-Convenient Drug Delivery

Physicians interviewed unanimously call for noninjectable MS therapies to replace the currently available injected drugs because, as one expert explains, "people don't like injecting themselves, and it's much more problematic if you're traveling or going to work to have to inject yourself." The need for noninjectable formulations is especially important as drug developers seek approval for use of their agents earlier in the disease process, when patients may have experienced only one demyelinating event and MRI evidence suggests MS. Physicians interviewed say that it is difficult to persuade patients with early-stage disease to adhere to an injection schedule when they are not noticeably afflicted by the disease. Nevertheless, although noninjectable formulations would enhance patient compliance, physicians interviewed do not see convenience as an acceptable trade-off for efficacy, as we discuss later in this report (see Chapter 6, "Emerging Oral Immunomodulatory Therapies"). "It's better to have an oral therapy versus an injected therapy, but the main point is efficacy. If you have a more efficacious drug, but it's injectable, it's better than a less-efficacious oral drug," states one French expert.

Attempts to develop inhaled or oral IFN-β therapies (Biogen Idec, Nektar Therapeutics [formerly Inhale Therapeutics], Merck Serono, Nastech Pharmaceutical) and an oral formulation of glatiramer acetate (Teva, Autoimmune) have been disappointing because of the drugs' poor or variable bioavailability. Although experts interviewed overwhelmingly express the need for oral therapies, most physicians agree that an inhaled or oral formulation of these disease-modifying agents is highly unlikely because all past attempts have proved futile; physicians interviewed believe that novel small-molecule therapies with oral formulations are the more promising prospect.

The majority of therapies slated to launch during our study period have oral formulations: cladribine, teriflunomide, FTY-720, BG-12, and laquinimod. These drugs will not replace IFN-βs or glatiramer acetate as first-line therapy. However, FTY-720 will be increasingly used second- or third-line behind these agents because of its demonstrated superior efficacy over that of other emerging therapies. The other oral emerging therapies have shown only

modest efficacy and safety thus far in clinical trials. We expect that BG-12 and laquinimod will be used third-line in early-stage MS following IFN-βs, glatiramer acetate, and FTY-720 and that cladribine and teriflunomide will be used third-line in aggressive RR-MS and SP-MS patients following IFN-βs and natalizumab. Although cladribine's twice-yearly dosing schedule provides greater convenience than other oral agents, concerns over its safety and efficacy will prevent it from being more widely used. Despite the advances in MS treatment these oral emerging therapies represent, additional oral therapies with superior efficacy and safety are still needed.

Improved Diagnostic Criteria

With the diagnosis of MS increasingly occurring at earlier stages of the disease, most experts call for diagnostic criteria that more clearly define the symptoms of MS because, as one expert explains, "By the time we make a diagnosis of MS, the disease is well-established. I think the first or presymptomatic diagnosis of MS remains a huge challenge."

Most experts interviewed agree that MS is a complex disease, and this complexity can make a proper and timely MS diagnosis difficult; clarification of what categorizes MS is needed as an initial step in diagnosing MS. One Italian expert explains, "What is really needed is more clarity in the definition of MS. The problem is that MS is many diseases under the umbrella of what we call MS. The improvement should be to categorize very, very strictly all the MS subcategories and try to find out what is really MS under a long-term follow-up, for instance, in order to exclude other MS-like diseases."

Because MS patients often initially present to physicians other than neurologists (e.g., general practitioners [GPs], primary care physicians [PCPs], ophthalmologists), experts interviewed stress that all nonspecialists must be educated about the symptoms of MS in order to correctly diagnose the disease in the early stages. "With other new challenges that we have, such as differential diagnosis with disseminated encephalomyelitis, neuromyelitis optica, clinically isolated syndrome, all these things are adding more difficulties to the early diagnosis of disease," notes one U.S. neurologist. "We have to train the GPs, ophthalmologists, urologists. That's most important," a German neurologist adds.

As more patients are diagnosed at earlier stages, experts interviewed note that the question of how the disease will progress becomes more essential to address. "The challenge would be to separate people who are going to be benign from people who are going to be aggressive in the short term so that you can start therapies accordingly," explains one Spanish expert, adding, "My problem is not being able to tell you whether you have MS but whether it will be aggressive." The types of therapies that a patient receives are influenced in large part by how MS will progress, but in early stages of the disease, the rate of progression is difficult to assess.

Experts interviewed assert that improvements in diagnosis may come from several sources, although most experts stress that diagnosis will still require the use of multiple criteria. Experts acknowledge that there are currently no reliable biomarkers of MS, but, as one expert points out, "With proteomics

and biomarker studies gaining momentum, you might identify a marker that might in theory allow you to diagnose MS fairly early." Although the utility of genetic biomarkers, such as the *HLA-DR2* and *-DR4* alleles, in MS diagnosis and treatment remains controversial, some experts assert that genetic differences that are related to immune regulation or regenerative potential may be beneficial in MS diagnosis.

Further clarification of MS symptoms, dissemination of that information to physicians, and use of additional criteria such as biomarkers will together promote correct diagnosis of MS at earlier stages.

Improved Animal Models

Only one MS animal model, experimental allergic encephalomyelitis (EAE), is broadly accepted by scientists; however, treatments based on this model "have failed and continue to fail. There have been at least 1,000 treatments for EAE. If you do a search on EAE and look at treatment, there are probably 1,000 ways you can treat EAE," notes one expert. Treatments that appear promising in EAE often do not translate into equivalent results in human MS. "It's easy to get excited about mouse experiments," warns another expert, "but you have to get into the patient to really know whether you're in business or not."

Expert consensus is that MS is a group of diseases, not a single disease, and that the EAE model does not represent all forms of MS. Most experts believe that the EAE model best illustrates the more progressive and degenerative forms of MS (such as PP-MS) and the more inflammatory forms (such as RR-MS) but not the progression from inflammatory to progressive MS that is seen in SP-MS patients.

In addition, animal models have a well-controlled (inbred) genetic background and do not represent the diverse genetic makeup of the human MS patient population. Because genetic profile influences the immune response in MS, favorable results in animal models do not necessarily translate into positive results in clinical trials with the general MS patient population. For this and other reasons, numerous efforts that have proved beneficial in rodent models have failed in the clinic. The lack of more robust and appropriate animal models will continue to hinder drug development and impede advancements in MS therapy and disease modification.

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Chapter 6

Emerging Oral Immunomodulatory Therapies

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.5401.2615 ♦ Fax +81.3.5401.2617

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6. Emerging Oral Immunomodulatory Therapies

Key Findings

- The launch of five oral agents during our forecast period will fulfill a significant unmet need in a market of injectables. However, physician concerns over these agents' safety and efficacy will limit their patient share, preventing their sales from outperforming those of current therapies.
- Novartis/Mitsubishi's FTY-720 (fingolimod) has generated much interest among experts interviewed because of its potent efficacy, acceptable safety, and oral formulation. FTY-720 will obtain the greatest market and patient shares of all emerging therapies during our forecast period because of its use in RR-MS (including aggressive RR-MS) and SP-MS.
- Immunomodulation and immunosuppression continue to be the primary focus of MS drug development. All oral therapies expected to launch during our forecast period will target some aspect of the autoimmune response.
- The safety profile of oral therapies will dictate which patient population receives them. A safe oral therapy will be widely used by early-stage MS patients, but an oral therapy with potentially severe side effects will be used only by patients with refractory disease or aggressive RR-MS.

"There is a trend in developing new oral therapies; a lot of new trials are coming up, ongoing. It is hugely convenient from the patient's point of view and avoids the unpleasantness of injections and injection-site reactions. There will be a huge initiative to develop orally effective treatment for multiple sclerosis."

—Neurologist, United Kingdom

Expert Commentary: Emerging Oral Immunomodulatory Therapies in Multiple Sclerosis, 2007

Drug	Expert Opinion
FTY-720 (Novartis/ Mitsubishi Pharma's fingolimod)	"Fingolimod appears to be really heading the pack so far as an interesting possibility [as an oral therapy]. The fact that it's going on to Phase III is a very, very important situation because that means that if the Phase III, two-year study shows positive results, then most likely the company is going to request of the FDA an accelerated approval, which means it can be available in four years or so." — Neurologist, United States
Laquinimod (Teva/ Active Biotech)	"It could be pretty much like interferon because it comes from the same class of drug because it's an immunomodulant drug, but, again, like interferon, it doesn't have [such] good effects on [disease] progression. So it's the same problem." — Neurologist, Italy
Teriflunomide (Sanofi-Aventis)	"There are some drugs currently in Phase III clinical studies such as FTY-720, which is a pill of course, that is very interesting. And the other very interesting drug is teriflunomide, which is very encouraging, and I think one of these two will help us to treat outpatients in the near future." —Neurologist, Germany
Oral cladribine (Merck Serono)	"The former experience with parenteral cladribine was a very positive one as regards the efficacy of treatment. So, if oral cladribine will keep the same efficacy profile as the original drug formulation, I think it might be, again, another option for patients." — Neurologist, Italy

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Pipeline Status of Key Multiple Sclerosis Drugs

Most Promising Emerging Therapies		
Drug	Launch Date	Peak-Year Sales Potential
FTY-720	2010	$750-1,000 MM
MBP-8298	2011	$250-500 MM
Daclizumab	2009	$100-250 MM
Oral cladribine	2010	$100-250 MM
In Development[a]:	Recently Discontinued:	
Phase III/Registered/Preregistered: 5	Phase II: 4	
Phase II: 21	Phase I: 6	
Phase I: 20		
Preclinical/Discovery: 28		
Key Targeted Mechanisms of Action:		
Monoclonal antibodies: 7		
Chemokine receptor antagonists: 7		
Oral immunosuppressants: 3		
Oral immunomodulators: 6		
Nonoral immunomodulators: 8		
VLA-4 modulators: 4		
Neuroprotective agents: 10		

a. The number of drugs in development includes oral and injectable immunomodulators and neuroprotective/remyelinating agents.

VLA = Very late antigen.

Note: Numbers given here are Decision Resources estimates for key agents based on review of multiple publicly available databases and information.

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Source: Decision Resources, Inc.

Overview

Although current disease-modifying drugs represent an improvement in the treatment of multiple sclerosis (MS), current therapies' methods of administration (injection or IV infusion) reduce patient compliance. As a result, drugs with oral formulations will have a significant market advantage over currently available injectable drugs when they reach the market. Several oral compounds are in clinical development for MS and are expected to launch during the 2005-2020 study period. None of these oral drugs is designed to reverse the disease but may be able to slow or prevent further disease progression.

All of the oral drugs in clinical development for MS modify the immune response, and this continued focus on the immune system as the primary drug development target is the result of several factors. Because the majority of MS patients (65%) have the relapsing-remitting form of the disease, which is characterized by immune attacks, pharmaceutical companies tend to direct

their research programs toward this patient population to provide a drug for the widest population possible, which in return will offset the high cost of bringing the drug to market. In addition, the immune response has been and continues to be extensively studied; as a result, more compounds that may have therapeutic potential are identified and pursued in clinical trials. Furthermore, an animal model that mimics the MS inflammatory response exists, although experts admit that this model is not optimal and compounds that demonstrate utility in these models do not always successfully translate into efficacious compounds in clinical trials.

The majority of oral compounds in development for MS are discussed at length in this chapter. Two additional oral compounds have limited information available and so are not discussed in detail; however, their mechanisms of action and preliminary clinical trial data are of interest and warrant comment. One such compound is interferon-tau (Tauferon), in development by Pepgen as an oral treatment for MS. Tauferon is structurally related to, but biologically distinct from, interferon beta (IFN-β). Phase II trials have been ongoing since August 2005. Phase I trials demonstrated that Tauferon induced a shift in the cytokine profile from proinflammatory (T_H1) to anti-inflammatory (T_H2) and was well tolerated by patients (n=16). Experts express concern that it will not be as effective as the current IFN-β therapies. "It's [Tauferon's] very harmless and it would be interesting to see how it works, but it would be a surprise if it really changed a lot in terms of disease progression," states one expert.

Another oral compound of note is SB-683699 (T-0047, firategrast), an alpha-4-integrin antagonist that Tanabe licensed to GlaxoSmithKline in 2000 for the treatment of MS and Crohn's disease (CD). Phase II trials were initiated in both indications in 2004. A randomized, placebo-controlled, dose-ranging study had enrolled 260 RR-MS patients to examine the efficacy of four doses of SB-683699 in reducing the number of new lesions as assessed by magnetic resonance imaging (MRI) scans; earlier Phase I data demonstrated that SB-638699 had bioactivity similar to that of natalizumab (Biogen Idec/Elan's Tysabri), also an alpha-4-integrin antagonist, at doses of 800 and 1,200 mg. However, in March 2005, the FDA suspended trials of all drugs in this class because of the development of progressive multifocal leukoencephalopathy (PML) in patients taking natalizumab in combination with IFN-β-1a (Biogen Idec's Avonex). An independent safety review board reported no evidence of immunosuppression or PML in any patients taking SB-683699, which is not chemically related to natalizumab because it is a small molecule instead of a monoclonal antibody. Clinical trials of SB-683699 resumed in January 2007.

Figure 6-1 lists select companies with drugs that are in development or have launched for MS.

Emerging Oral Therapies Positioning

The competition to develop oral disease-modifying drugs for MS is intense because a convenient formulation would fulfill a significant unmet need in a market of injectable drugs; however, none of the oral agents now in development has yet demonstrated superior safety and equivalent efficacy over currently available therapies. Therefore, none will be able to supplant

Figure 6-1

Select Multiple Sclerosis Franchises, 2007

Company	Preclinical	Phase I	Phase II	Phase III	Preregistered	Launched
Biogen Idec	Lingo/TRAIL	CDP-323	Rituximab (RR-MS), daclizumab	Rituximab (PP-MS), BG-12		Avonex, natalizumab
Bayer Schering Pharma/ Berlex			Alemtuzumab, fludarabine	500 mg Betaseron		Betaseron
Merck Serono	Osteopontin	MMP-12 inhibitor, JNK inhibitor		Oral cladribine, reformulated Rebif		Rebif, mitoxantrone
Pfizer	CCR2 research program					Rebif
Teva	TV-3606		Laquinimod, TV-5010	40 mg glatiramer acetate		Glatiramer acetate
Millennium			MLN-1202			
Sanofi-Aventis				Teriflunomide		
Novartis				FTY-720		

CCR2 = Chemokine receptor-2; IFN = Interferon; PP-MS = Primary progressive multiple sclerosis; RR-MS = Relapsing-remitting multiple sclerosis; SP-MS = Secondary progressive multiple sclerosis.

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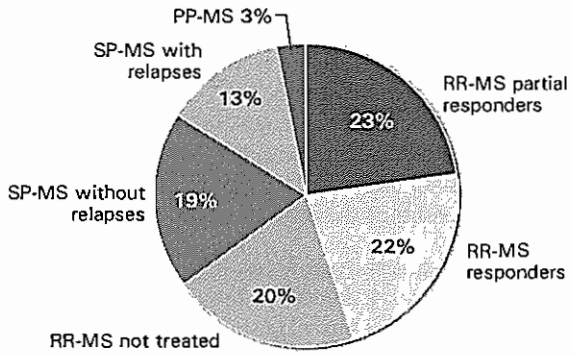
IFN-β (Bayer Sehering Pharma's Betaferon/Berlex's Betaseron, Biogen Idee's Avonex, and Merck Serono [formerly Serono]/Pfizer's Rebif) or glatiramer acetate (Teva Pharmaceuticals' Copaxone) as the leading treatment for RR-MS during our study period. Natalizumab, which has efficacy superior to that of other current therapies but is hampered by severe side effects (PML), is indieated for RR-MS patients but is in fact prescribed only to patients with aggressive RR-MS.

Patients with early-stage MS will, in particular, welcome oral agents; beeause these patients have a mild form of the disease, many are reluctant to undertake an onerous self-injection treatment regimen. However, experts interviewed state that they will prescribe oral therapies over current injectables only if they are safe, particularly to the early-stage MS population, who may not want to risk severe side effects when they have only mild symptoms. If emerging oral agents are associated with severe side effects, they will likely be used third- or fourth-line behind the IFN-βs, glatiramer acetate, and, in some cases, natalizumab in patients with aggressive RR-MS or in patients whose disease is refractory to current therapies (see Figure 6-2 for a summary of MS patient segmentation). Such patients may be more willing to accept a less benign safety profile if a drug demonstrates even modest efficacy, particularly if the patients have exhausted all other therapeutic options.

Most oral agents expected to reach the market during our forecast period (Merck Serono's oral cladribine [Mylinax], Sanofi-Aventis's teriflunomide, Biogen Idec's BG-12, and Teva/Active Biotech's laquinimod) have only modest efficacy and safety profiles and thus will be limited to second- or

Figure 6-2

Multiple Sclerosis Patient Populations, 2007



PP-MS = Primary-progressive multiple sclerosis; RR-MS = Relapsing-remitting multiple sclerosis; SP-MS = Secondary-progressive multiple sclerosis.

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third-line use behind current therapies in niche populations. Novartis/ Mitsubishi Pharma's FTY-720, which we expect to launch in the second half of 2010, has the greatest market potential of all emerging therapies because of its oral formulation, demonstrated efficacy, and acceptable safety profile.

Concerns over a drug's safety are the result of the opportunistic infections that occurred with natalizumab/Avonex use (see Chapter 4, "Current Therapies and Treatment Trends"); to potentially avoid such severe side effects, companies such as Merck Serono are investigating immunomodulatory therapies administered in a pulse. Theoretically, a pulse of immunosuppressant therapy will temporarily eliminate both immune and autoimmune cells but allow the immune system to recover sufficiently to fight any infections that may occur (as opposed to chronic suppression of the immune system, which prevents the immune system from mounting a response). Moreover, because autoimmune cells recover more slowly than the rest of the immune system, RR-MS patients should theoretically not suffer relapses caused by autoimmune cells after a pulse of immunosuppressant therapy. Thus, following a pulse of immunosuppressant therapy, the RR-MS patient should have a normally reconstituted immune system capable of fighting infections, without the autoimmune cells that cause relapses. However, it is unclear whether pulsed therapies will offer protection from opportunistic infections and whether such an administration regimen will effectively prevent relapses in RR-MS.

Because the cases of PML were reported in patients taking a combination of natalizumab and Avonex, experts interviewed have become wary of prescribing a combination of disease-modifying therapies. Despite this

concern, companies such as Merck Serono and Sanofi-Aventis are exploring use of their respective oral emerging therapies in combination with current therapies. Given that little information on these combination trials is available and that physicians are wary of combination therapy, we do not forecast any combination use of disease-modifying drugs for MS over the course of our study period.

Keys to success for emerging oral therapies include increasing overall drug-treatment rates (including the treatment of patients with early-stage MS, niche patient populations [e.g., patients with aggressive RR-MS, patients who do not respond to currently available therapies], and of patients who have abandoned therapy) and stealing patient share from current therapies as a result of their greater convenience.

Several companies have oral MS therapies in clinical trials, and these agents are discussed in detail in this chapter; four additional compounds are in preclinical stages. Table 6-1 summarizes the oral immunomodulatory drugs in development for MS that are profiled in this chapter, and Table 6-2 outlines Decision Resources' estimates of launch dates for key emerging therapies. Figure 6-3 outlines oral drugs in all phases of development for MS.

Oral Immunomodulators

Overview

As mentioned, competition is intense in the development of oral formulations of disease-modifying drugs because convenient formulation represents an area of high unmet need in the MS market. The oral formulation of Teva's glatiramer acetate promised more-convenient drug delivery, but the company halted development in March 2006 after disappointing efficacy results.

Novartis's FTY-720 (fingolimod, outlined below) is the only oral sphingosine-1-phosphate (S1P) receptor modulator in clinical trials for MS. Several companies, such as Kyorin, Actelion/Roche, and EPIX/Amgen, have developed S1P receptor modulator research programs and are conducting preclinical studies. FTY-720 is the most serious threat to current therapies because it has demonstrated efficacy and has an acceptable safety profile.

Biogen Idec is developing BG-12, an oral, second-generation fumarate derivative for the treatment of RR-MS. Teva Pharmaceuticals and Active Biotech are also developing an oral immunomodulator, laquinimod (SAIK-MS). We outline both drugs in detail later in this section.

The oral immunomodulator pirfenidone (Deskar) was originally in development by Marnac and Bayer Schering Pharma for the treatment of progressive forms of MS (SP-MS and PP-MS); Bayer Schering Pharma discontinued its involvement and returned all developmental rights to Marnac in 2003. Pirfenidone is an inhibitor of the p38 mitogen-activated protein (MAP) kinase, an enzyme that is expressed in T cells and is involved in leukocyte recruitment and the production of inflammatory mediators such as proinflammatory cytokines. The only data available so far are from a Phase I trial (Bowen JD, 2003). Results of a one-year, open-label dose-escalation trial reported in 2002 demonstrated that the maximum dose reached by

Table 6-1

Emerging Oral Immunomodulatory Therapies in Development for Multiple Sclerosis, 2007

Compound	Status	Marketing Company	Peak-Year Sales Potential[a] ($MM)
Oral immunomodulators			
FTY-720			750-1,000
United States	III	Novartis/Mitsubishi Pharma	
Europe	III	Novartis/Mitsubishi Pharma	
Japan	—	—	
BG-12			100-250
United States	—	—	
Europe	III	Biogen Idec[b]	
Japan	—	—	
Laquinimod			100-250
United States	II	Teva Pharmaceutical/Active Biotech	
Europe	II	Teva Pharmaceutical/Active Biotech	
Japan	—	—	
Simvastatin			Lack of data precludes estimate
United States	II	Merck & Co.	
Europe	—	—	
Japan	—	—	
Oral immunosuppressants			
Teriflunomide			100-250
United States	III	Sanofi-Aventis	
Europe	—	—	
Japan	—	—	
Oral cladribine (Mylinax)			100-250
United States	III	Merck Serono[c,d]	
Europe	—	—	
Japan	—	—	
Europe	—	—	
Japan	—	—	

a. Represents peak-year sales in the major pharmaceutical markets for the indication under study only. Methodology is explained in the "Emerging Immunomodulatory Therapies" chapter of the text.
b. BG-12 was originally in development by Fumapharm, which was acquired by Biogen Idec in May 2006.
c. In January 2007, Merck KGaA acquired Serono and renamed the company Merck Serono.
d. Merck Serono acquired oral cladribine from Teva Pharmaceutical, which continues to receive milestone payments for development of the drug.

Note: Status is based on databases such as R&D Insight and the Investigational Drugs Database (IDdb); periodicals such as *Scrip*, the FDC's *Pink Sheet*, and *Marketletter*; company reports and press releases; and industry contacts.

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Source: Decision Resources, Inc.

Table 6-2

Estimated Launch Dates for Key Late-Stage Emerging Therapies for the Treatment of Multiple Sclerosis, 2007

Drug	United States	France	Germany	Italy	Spain	United Kingdom	Japan
Daclizumab	2009	2010	2010	2010	2010	2010	—
Oral cladribine	2010	2010	2010	2010	2010	2010	—
FTY-720	2010	2011	2011	2011	2011	2011	2020
MBP-8298	2011	2011	2011	2011	2011	2011	—
Teriflunomide	2011	2012	2012	2012	2012	2012	—
BG-12	2012	2011	2011	2011	2011	2011	—
Laquinimod	2012	2012	2012	2012	2012	2012	—

Note: Launch dates are estimated based on an analysis of the product's current phase of development, development timelines for the disease, company reports and estimates, expert opinion, status of development or marketing collaborations, and analyst reports.

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Source: Decision Resources, Inc.

20 patients with progressive MS was 2,400 mg/kg. Patients' Expanded Disability Status Scale (EDSS) scores stabilized, but their scores on the Scripps Neurologic Rating Scale worsened slightly. MRI lesion results varied: three patients had improved plaques and two patients had worse plaques after one year of treatment. The treatment did not seem to reduce the number of active plaques because, among the 20 patients, 14 gadolinium (Gd)-enhaneing plaques (indicating active lesions) were detected after one year and 8 were detected at baseline. In addition, 5 of the 20 patients had to reduce their doses of pirfenidone because of nausea. Although the company appeared to be conducting additional trials for MS in 2004, no additional information on pirfenidone's development for this indication is available; pirfenidone continues to be in development for idiopathic pulmonary fibrosis. These data do not bode well for the launch of this drug for MS; even if the drug has an oral formulation for an underserved patient population, it does not appear to be very efficacious, nor does it have a good tolerability profile

Figure 6-3

Pipeline Status of Oral Drugs by Class for Multiple Sclerosis

Key Classes	I	II	III
Oral immunosuppressants		●	●●
Oral immunomodulators	●	●●	●●

● = one drug.

Note: Numbers reported here are Decision Resources estimates of key agents covered in this report based on review of multiple publicly available databases and information.

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relative to currently available immunomodulators. Therefore, we do not foresee the launch of pirfenidone for the treatment of progressive MS.

Bayer Schering Pharma's oral phosphodiesterase-4 (PDE-4) inhibitor mesopram (ZK-117137) was in development for inflammation in MS. Mesopram affects the cytokine profile of autoimmune T cells by switching from the proinflammatory T_H1 profile to the anti-inflammatory T_H2 profile. In addition, the drug may reduce the blood-brain barrier (BBB) permeability and thereby reduce T-cell infiltration into the CNS (Folcik VA, 1999). The drug completed Phase IIa clinical trials to assess the safety and tolerability of doses up to 1 mg/day in RR-MS and SP-MS patients; disease progression was to be assessed by MRI. However, in February 2005, Bayer Schering Pharma discontinued mesopram's development and decided to shift resources away from this project.

Minocycline (Lederle Rx's Minocin, generics), a second-generation tetracycline, is being studied for MS at the University of Calgary in Canada. Minocycline is reported to inhibit several proteinases, including the matrix metalloprotcinase protein 9 (MMP-9), which is thought to facilitate T-cell infiltration into the CNS by breaking down a segment of the BBB (Brundula V, 2002). Minocyclinc also reduces T-cell and macrophage activity, including the production of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) (Giuliani F, 2005b). Clinical data are lacking, but the drug's mechanism of action is promising, and minocycline could be used off-label as an add-on to current therapies for RR-MS. Indeed, in experimental autoimmune encephalomyelitis (EAE), a rodent model of MS, minocycline in combination with either glatiramer acetate or IFN-β attenuated the severity of the disease to a greater extent than minocycline treatment alone (Giuliani F, 2005c; Giuliani F, 2005a). A Phase II trial has begun enrolling patients to examine the efficacy of minocycline as an add-on therapy to Rebif for RR-MS. Because minocycline is available as a generic drug, we do not expect pharmaceutical companies to finance costly clinical trials that would yield a poor return on their investment. Therefore, we do not foresee the launch of this therapy for the treatment of RR-MS.

Statins have immunomodulatory effects in addition to their more-well-known cholesterol-lowering effects; therefore, statins may have a disease-modifying effect on the progression of MS. Several statins are being investigated for the treatment of MS, including pravastatin (Bristol-Myers Squibb's Pravachol, generics) for RR-MS and atorvastatin (Pfizer's Lipitor/Tahor/Sortis/Torvast/Cardyl) for early-stage MS (clinically isolated syndrome). We discuss simvastatin (Merck's Zocor) in this section because it is the most advanced in development for MS.

Mechanism of Action

FTY-720 alters lymphocyte trafficking by preventing their exit from lymph nodes, so that the cells are sequestered in nodes and in Peyer's patches (lymph nodes located in the intestine) and are unable to enter the CNS, thus preventing inflammatory damage to myelin. Preclinical data suggest that FTY-720, in addition to its immunomodulatory role, may function as a neuroprotectant by inhibiting the production of inflammatory mediators

called eicosanoids. FTY-720's inhibition of eicosanoid production theoretically dampens the immune response that causes demyelination.

BG-12 and laquinimod have immunomodulatory actions because the drugs appear to inhibit macrophage infiltration to the CNS. BG-12's mechanism of action appears similar to that of Millennium's chemokine reeeptor antagonist MLN-1202 (see Chapter 7, "Emerging Injectable Immunomodulatory Therapies") and may be associated with a similar side-effect profile—specifically, the development of opportunistic infections. Likewise, laquinimod appears to function similarly to a related compound, roquinimex (Pfizer's Linomide), and as a result may be associated with the same severe cardiac adverse effects, although laquinimod is being investigated at a much lower dose (0.1 mg and 0.3 mg compared with 1, 2, 5, and 7.5 mg).

Statins interfere with mediators of inflammation and appear to inhibit leukocyte accumulation in the CNS. Statins have multiple immunomodulatory effects; research suggests that they change the cytokine profile of T cells from the proinflammatory T_H1 profile to the anti-inflammatory T_H2 profile (Youssef S, 2002). In addition, statins inhibit proteins essential for leukocyte infiltration into the CNS (notably the T-cell-associated integrin leukocyte function antigen [LFA-1] and MMP-9) and should therefore reduce inflammation in MS, thereby slowing disease progression. Finally, in EAE rodent studies, lovastatin (Merck & Co.'s Mevacor; Andrx's Altocor/Altoprev) ameliorated EAE symptoms (Stanislaus R, 2001). It is important to note, however, that many EAE study results have not translated as expected in humans.

FTY-720

Novartis is developing FTY-720 (fingolimod) under license from Mitsubishi Pharma. The company was developing the drug for transplantation patients, but it failed to meet its primary end point in two Phase III transplantation studies and was discontinued for this indication in the United States and Europe; the drug is still in Phase II development for this indication in Japan. In addition to MS, the company is developing FTY-720 for the treatment of CD, ulcerative colitis (UC), and inflammatory bowel disease (IBD). Novartis completed a six-month Phase II MS trial in June 2005 and has completed an 18-month extension phase. Two Phase III trials were initiated in 2006; prior to the initiation of these trials, the company, after discussions with the FDA, evaluated safety data of FTY-720 in transplantation studies. The first trial began in January 2006 and is evaluating the efficacy of FTY-720 in RR-MS patients; the second trial began in May 2006 and is examining the drug's efficacy compared with that of Avonex in patients with RR-MS.

FTY-720 is rapidly phosphorylated in vivo and binds the S1P receptor expressed by T cells present in lymph nodes; this receptor is necessary for the exit of activated T cells from lymph nodes. Upon FTY-720 binding, the S1P receptors are internalized and degraded and therefore unavailable for activated T-cell exit from lymph nodes. Thus, T-cell infiltration into the CNS is reduced, thereby preventing inflammatory damage to myelin. Unlike natalizumab, FTY-720 has a short half-life, so its effects are rapidly

reversible. As a result, the agent may have a better safety profile than that of natalizumab where PML is concerned.

A six-month Phase II study completed in June 2005 showed that FTY-720 significantly reduced the mean number of Gd-enhancing lesions at six months (Kappos L, 2006a). This double-blind, placebo-controlled study enrolled 281 RR-MS patients to test the efficacy of once-daily oral 1.25 mg (n=93) or 5 mg (n=92) FTY-720 compared with placebo (n=92) for six months, followed by an open-label extension phase slated to last for six months (during which patients either continued treatment on their dose or, if they had received placebo during the first six months, would be randomized to receive either 1.25 or 5 mg doses of FTY-720). Patients were required to have had at least two documented relapses during two years before enrollment, at least one documented relapse during the last year, or a positive Gd-enhanced MRI scan at screening. The study's primary end points included the total number of Gd-enhancing lesions as assessed by monthly MRI seans as well as the safety and tolerability of the two doses of FTY-720. Secondary end points included additional MRI measures as well as relapse rates, time to first relapse, the proportion of relapse-free patients, and disability as measured by EDSS.

FTY-720 redueed the number and volume of Gd-enhancing lesions after six months of treatment (Kappos L, 2006a); these results bode well for future studies of FTY-720. The mean number of Gd-enhancing lesions fell 42% in patients treated with 1.25 mg FTY-720 compared with placebo, while the mean number of Gd-enhancing lesions fell 88% in patients on 5 mg FTY-720. Similarly, treatment with FTY-720 reduced the mean volume of Gd-enhancing lesions by 66% and 86% for the 1.25 and 5 mg doses, respectively, compared with placebo at six months.

Other therapeutic benefits, including elinical measures, were observed with both doses of FTY-720, although the level of improvement was not statistically different between the two doses, reflecting the lack of a dose-response eurve (Kappos L, 2006a). The percentage of patients who were lesion-free was significantly improved with treatment at both doses (77% of patients treated with 1.25 mg FTY-720 and 82% of patients treated with 5 mg FTY-720) at six months, compared with patients who received placebo (47%). MRI observations correlated with clinical improvement: 55% and 53% reductions in the annualized relapse rate were noted for FTY-720 doses of 1.25 mg and 5 mg, respectively. Similarly, the number of patients who were relapse-free at six months was greater in the treated group than in the placebo group. Indeed, 86% of FTY-720-treated patients (both doses) were relapse-free at six months, compared with 66% of placebo-treated patients. The time to first relapse was also significantly lengthened in treated patients compared with patients on placebo. No significant differences were observed in EDSS score with FTY-720 treatment compared with placebo.

Overall, the lower dose of FTY-720 was generally well tolerated, and although 84% of treated patients experienced at least one adverse event, this percentage was not different from placebo (82%); the higher dose of FTY-720 had a higher incidence of adverse effects (96%), which was statistically significant from placebo (Kappos L, 2006a). Adverse events were

generally mild; nose, throat, and influenza infections were the most common. Infections and gastroenteritis occurred in 34% and 44% of patients on 1.25 mg and 5 mg FTY-720, respectively (compared with 20% for placebo). Other side effects included diarrhea, nausea, abdominal pain, somnolence, fever, back pain, shortness of breath, and hypertension.

No severe infections were reported in FTY-720-treated patients, but serious adverse effects occurred more often in patients on the high dose of FTY-720 (14 instances), compared with lower doses and placebo (8 and 4 instances, respectively). One patient on 5 mg FTY-720 developed posterior reversible encephalopathy syndrome, a reversible neurological disorder associated with changes in blood pressure that is characterized by headache and vision changes. FTY-720 also induced abnormal lab readings, including low white blood cell count (leukopenia) in 2% and 5% of patients on 1.25 mg and 5 mg doses of FTY-720, respectively, compared with no cases with placebo, as well as an elevation in liver enzymes, which could indicate damage to the organ. Although instances of cardiac (including bradycardia, which had also been noted in Phase III transplant studies) and pulmonary events were reported in treated patients, they occurred in less than 5% of patients, most of whom received the 5 mg dose, and were not severe enough to cause clinical concern.

Although the extension phase of this Phase II trial was planned to last six months, the company extended the phase by 12 months, and results at the end of the 18-month total extension period demonstrated that FTY-720 maintained its efficacy throughout the entire two-year study period. Results presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) held in Madrid, Spain, in September 2006 showed that in patients who received FTY-720, the number of new lesions was reduced by 80%, as assessed by MRI, and up to 77% of patients remained relapse-free during the study. Patients who received placebo during the initial six-month period experienced improvement after switching to FTY-720, as measured by MRI and clinical end points. Two infections were reported in patients who switched from placebo to FTY-720: herpes zoster in a patient who received 5 mg FTY-720 and enterocolitis in a patient who received 1.25 mg. The incidence of adverse effects was not different from the core six-month study.

Based on the positive results of the Phase II study, Novartis initiated a Phase III study in January 2006 in RR-MS patients. Because the Phase II data indicated that the lower dose (1.25 mg) of FTY-720 had slightly better efficacy than the higher dose (5 mg), as well as a lower incidence of adverse effects, the company chose the lower dose to be further evaluated in this study and is not pursuing the higher dose. The FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) trial is a randomized, double-blind, placebo-controlled study examining the efficacy of once-daily FTY-720 (0.5 or 1.25 mg doses) compared with placebo. The trial will include 2,000 RR-MS patients and is slated to last two years. A second randomized, double-blind Phase III study (Trial Assessing Injectable Interferon vs. FTY720 Oral in RR-MS [TRANSFORMS]) was also initiated in 2006; it is investigating the efficacy of FTY-720 (0.5 mg and 1.25 mg

doses) compared with once-weekly injections of Avonex in 1,000 RR-MS patients for 12 months.

Physicians interviewed express concern about the side-effect profile of FTY-720, particularly the possibility of developing opportunistic infections, including PML, but also cases of macular edema and pulmonary fibrosis observed in transplant patients treated with FTY-720. Yet, given the results of Phase II trials, physicians are cautiously optimistic about the drug's safety in future trials. As one Italian physician states, "The only concern is that at the end of the day we now know that interferons and Copaxone are safe, and we know this from the experience of ten years of treatment almost all over the world. For fingolimod, of course, we will have to wait for the so-called Phase IV experience before achieving the same conclusions." However, experts are excited at the success of FTY-720 in Phase II trials and are hopeful of its continued success in Phase III trials. According to one expert, "Fingolimod appears to be really heading the pack so far as an interesting possibility [as an oral therapy]. The fact that it's going on to Phase III is a very, very important situation because that means that if the Phase III, two-year study shows positive results, then most likely the company is going to request accelerated approval from the FDA, which means it can be available in four years or so."

Addressing safety concerns is paramount to the success of FTY-720: as with all drugs that suppress the immune system, there is an increased risk of opportunistic infections with FTY-720 use, although FTY-720 may have a better safety profile than most immunomodulators. The cases of PML that were reported in patients taking natalizumab have heightened physicians' concern about such severe side effects and raise the issue of whether a drug's risks outweigh its therapeutic benefits. Indeed, at the FDA's request, Novartis reviewed its safety data from transplantation studies with FTY-720 prior to beginning Phase III trials in MS. In addition, preclinical data indicate that, in animal models, not all T cells are depleted by FTY-720 treatment, and B cells, as well as specific T-cell subtypes, retain their ability to be activated in response to viral infection (Brinkmann V, 2004; Fujino M, 2003; Pinschewer DD, 2000; Schuurman HJ, 2002). These data suggest that MS patients taking FTY-720 will retain the ability to fight infections, thus reducing the risk of severe infections.

Phase II data showed that FTY-720's safety profile is poorer than that of the IFN-βs but not worse than that of natalizumab, and the drug's convenient oral formulation will not outweigh the requirements of safety and efficacy. Thus, the Phase III FREEDOMS and TRANSFORMS trials are essential to assessing the safety and efficacy of FTY-720. If in Phase III trials FTY-720 demonstrates efficacy similar to that in Phase II (i.e., effects on relapse rate but not EDSS), the drug will likely be used second- or third-line following the IFN-βs and glatiramer acetate but selected over natalizumab. However, if FTY-720 treatment improves EDSS in addition to maintaining the improvement in relapse rate, the drug will likely be used second-line in RR-MS. Even if FTY-720's head-to-head evaluation with Avonex (the TRANSFORMS trial) shows that FTY-720 is superior to Avonex, safety concerns will hamper its use; therefore, the drug will not outperform IFN-βs. In addition, if FTY-720 continues to be safer than natalizumab, it will steal market share from natalizumab even if its efficacy is slightly lower.

We anticipate that FTY-720 will launch in the second half of 2010 in the United States, in 2011 in Europe, and in 2020 in Japan. Novartis intends to position FTY-720 first for RR-MS patients; it will be used primarily in RR-MS patients who have failed IFN-β or glatiramer acetate and who are wary of natalizumab's side effects. It may also enjoy limited use in patients with early-stage MS who are reluctant to self-inject and in patients with aggressive RR-MS. FTY-720 will also garner patient share in the CP-MS population, particularly those SP-MS patients who continue to relapse; FTY-720 will likely be used second-line behind the IFN-βs and will compete with daclizumab in this population. In addition, it is unlikely that FTY-720 will be used as part of a combination therapy because of the risk of opportunistic infections. Given its efficacy, acceptable safety profile, and oral formulation, we estimate FTY-720 will achieve peak-year sales of $750 million to $1 billion.

BG-12

Biogen Idec is developing the oral, second-generation fumarate derivative BG-12 for the treatment of RR-MS. This compound was previously in development by both Biogen Idec and Fumapharm, from which Biogen Idec had acquired the rights to develop and market a second-generation fumaric acid derivative in October 2003. Biogen Idec announced its intention to acquire Fumapharm and assume sole responsibility for developing and marketing BG-12 in May 2006. The drug was preregistered for the treatment of moderate to severe psoriasis patients in Germany in 2005; no additional information on the status of BG-12 in psoriasis is available. Biogen Idec announced in January 2007 the initiation of two Phase III trials in MS in Europe and stated that these trials will be extended to include U.S. sites later in the year.

BG-12 (also known as dimethyl fumarate) has been shown to reduce macrophage-induced inflammation in the spinal cord in the EAE model of MS (Schilling S, 2006). BG-12 also increased expression of the anti-inflammatory cytokine IL-10 and reduced expression of proinflammatory cytokines such as TNF-α and IL-6 (Schilling S, 2006; Wierinckx A, 2005).

The two Phase III trials initiated in 2007, Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS (DEFINE) and Comparator and an Oral Fumarate in Relapsing-Remitting MS (CONFIRM), are slated to enroll more than 2,000 patients worldwide. These randomized, double-blind, placebo-controlled studies will assess the efficacy and safety of BG-12 and are expected to run for two years. End points include relapse rate, disability progression, and MRI measurements. In addition, the CONFIRM trial will compare BG-12's efficacy with that of glatiramer acetate.

In January 2006, Biogen Idec and Fumapharm announced positive results from a Phase II study conducted in Europe; details of the study were announced in May 2006. The double-blind, placebo-controlled study investigated the efficacy of three doses of oral BG-12 (120 mg, 360 mg, and 720 mg) administered daily for six months in 257 RR-MS patients. The primary end point was the total number of Gd-enhancing lesions as measured

by MRI at six months of treatment compared with placebo. The number of new lesions and relapse rate were also examined.

BG-12 demonstrated a dose-dependent effect on clinical end points; only the highest dose (720 mg) elicited a statistically significant effect compared with placebo. This dose of BG-12 was also the most efficacious in Phase II trials in psoriasis; as a result, Phase III trials in this indication included only the 720 mg dose. It is likely that the company will continue to use this dose in Phase III trials for RR-MS. BG-12 reduced the number of Gd-enhancing lesions in RR-MS patients by 69% compared with placebo after six months of treatment. The number of newly enlarging T2-hyperintense lesions (which indicate areas of inflammation) was reduced by 48%, and relapse rate declined by 32% in the 720 mg BG-12-treated group compared with placebo. The most commonly reported adverse events were gastrointestinal side effects, flushing, headache, and nasopharyngitis. Elevation of liver enzymes was also noted. Infection rates were similar among treatment groups and no opportunistic infections were reported.

Neurologists interviewed by Decision Resources have mixed opinions regarding BG-12's potential to treat RR-MS. Some are enthusiastic because of the drug's oral formulation and the positive results from Phase II trials. Others are skeptical, noting that fumaric acid esters have been available in Germany since 1994 but have not engendered significant interest in other markets. If Phase III trials results demonstrate BG-12's continued safety and efficacy, the drug will likely be used for early-stage MS patients who do not want to begin an onerous injection schedule. We expect this drug to launch in 2011 in Europe and 2012 in the United States; seven-market peak-year sales will be in the $100-250 million range.

Laquinimod

Laquinimod (SAIK-MS) was originally developed by Active Biotech as an oral therapy for MS. Active Biotech successfully completed Phase II trials in Europe and Russia in 2003. The company then licensed the worldwide rights to develop and market laquinimod to Teva Pharmaceuticals in June 2004, although Active Biotech retains rights to laquinimod in the Nordic and Baltic countries. Active Biotech and Teva submitted an investigational new drug (IND) application to the FDA in June 2005; a Phase II trial was completed in the United States in August 2006. Teva initiated a Phase IIb trial in the first half of 2005 in several European countries as well as Israel and Russia and announced positive results in September 2006. Phase III trials are planned in both Europe and the United States, and the companies are in discussions with regulatory agencies concerning the design of these studies. Preclinical studies are also investigating the use of laquinimod in other autoimmune inflammatory diseases, including RA and IBD.

Laquinimod is a synthetic immunomodulator that is structurally related to roquinimex (Pfizer's Linomide). In the EAE model of MS, laquinimod has been shown to inhibit T-cell infiltration into the CNS (Brunmark C, 2002; Yang JS, 2004). Laquinimod also shifts the T-cell cytokine expression from the T_H1 proinflammatory cytokine profile to the T_H2 anti-inflammatory profile (Yang JS, 2004).

A randomized, double-blind, placebo-controlled Phase II study investigated the safety and efficacy of two doses of oral laquinimod (0.1 mg or 0.3 mg once daily) for relapsing MS (Polman C, 2005). A total of 209 patients were enrolled; criteria for enrollment included an EDSS score between 0 and 5.5 and at least one clinical exacerbation in the previous year or two exacerbations in the previous two years. Both RR-MS (n=177) and SP-MS (n=32) patients were included in this study. The primary end point was the cumulative number of active lesions at 24 weeks of treatment. Secondary end points included the number and volume of active lesions at weeks 8, 16, and 24 of treatment (as assessed by MRI), the number of exacerbations over the 24-week period, and safety. The study also included a follow-up MRI assessment eight weeks after treatment completion.

The higher dose of laquinimod (0.3 mg) showed statistically significant efficacy over placebo in reducing the number of active lesions; results with the lower dose of the drug (0.1 mg) were intermediate to the other treatment groups. Although this finding suggests that laquinimod acts in a dose-dependent manner, results with the 0.1 mg dose were not significantly different from the other treatment groups. Laquinimod treatment (0.3 mg) reduced the number of active lesions by 44% (5.24 lesions per laquinimod-treated patient compared with 9.44 lesions per placebo-treated patient) at 24 weeks of treatment. Interestingly, laquinimod-treated patients who had a higher number of active lesions at baseline demonstrated a greater response to the drug. There was no difference in response to laquinimod between RR-MS and SP-MS patients.

Laquinimod also demonstrated efficacy in reducing lesion activity (Polman C, 2005). The agent reduced the number of patients with active lesions throughout the 24-week treatment period: 20.6% of laquinimod-treated patients had active lesions versus 36.5% of placebo-treated patients. The percentage of patients who had no active lesions during the study period also improved with laquinimod: 30.2% given laquinimod compared with 22.2% given placebo.

Although it was effective at reducing the number of active lesions, laquinimod treatment did not lower the number of exacerbations or the number of patients who experienced exacerbations. In addition, EDSS score and quality-of-life measurements were not significantly different from placebo. Future studies must demonstrate that laquinimod is efficacious in multiple aspects of MS for the drug to achieve market success.

Laquinimod was generally well tolerated; the incidence of adverse effects was similar among the treatment groups. Four severe adverse effects were reported during the course of the study, one each in the placebo-treated and 0.1 mg laquinimod-treated groups and two in the 0.3 mg laquinimod-treated group. In addition, two adverse effects were noted during the follow-up period in the 0.3 mg-treated laquinimod group. Adverse effects included infections and, in the case of the 0.1 mg laquinimod patient, a brain contusion. Additional side effects included elevated liver enzymes and abnormal erythrocyte sedimentation rate (a nonspecific measure of inflammation). Importantly, laquinimod treatment did not increase the incidence of myocardial infarction, an adverse effect that was noted with

roquinimex that resulted in that drug's discontinuation in Phase III trials for MS.

Teva announced positive results from a Phase IIb trial in RR-MS patients in September 2006. The randomized, double-blind, placebo-controlled study examined the efficacy of two doses of laquinimod (0.3 mg and 0.6 mg daily) in approximately 300 RR-MS patients in Israel and eight European countries over 36 weeks. Because the previous Phase II data indicated that that trial's higher dose (0.3 mg) of laquinimod had slightly better efficacy than the lower dose (0.1 mg), Teva chose to pursue development with the higher dose. Teva and Active Biotech also examined a higher dose (0.6 mg) to identify an optimal dose with superior efficacy and safety. Laquinimod treatment reduced the number of Gd-enhancing lesions as well as the number of clinical relapses after 36 weeks; the 0.6 mg dose demonstrated significant improvement over placebo. The drug had a safety profile similar to that in previous studies. Many of the enrolled patients are continuing treatment in a blinded extension phase of this study, which is expected to last nine months.

Experts interviewed are intrigued by laquinimod because of the efficacy demonstrated in Phase II trials as well as its oral formulation. However, they stress, laquinimod must demonstrate efficacy in slowing disease progression for it to be competitive with current therapies, and they remain concerned that severe side effects, namely cardiac toxicity, could develop.

The efficacy of laquinimod in reducing lesion number and relapse frequency in Phase II trials holds promise for the drug; however, laquinimod must also show efficacy in slowing clinical disability as measured by EDSS and Multiple Sclerosis Functional Composite (MSFC) scores. Many experts indicate that slowing disability progression is the primary criterion for drug efficacy in clinical trials, and we expect Teva to include disability progression as an end point in Phase III trials. Laquinimod must also continue to have a tolerable safety profile through Phase III trials.

Although Active Biotech's Phase II trial included both RR-MS and SP-MS patients, Teva elected to enroll only RR-MS patients. The number of SP-MS patients enrolled in Active Biotech's study was small (15% of the total), and these patients were evenly distributed across the three treatment groups. Because no treatment differences were noted between these two MS subtypes and given the large percentage of MS patients who are considered relapsing-remitting, we expect future trials to include only RR-MS patients.

Phase III trials must show that laquinimod is both efficacious in delaying disease progression and safe for it to be a moderate competitor in the MS market. Given its modest efficacy thus far, we expect that laquinimod will be used primarily in early-stage MS patients who do not wish to begin injection therapy. Interestingly, although Teva and Active Biotech will likely position laquinimod as a monotherapy, preclinical studies have shown that combination therapy of laquinimod and IFN-β produced a synergistic effect on inhibiting disease development in the EAE model (Runstrom A, 2006). Even if laquinimod proves safe and synergistically efficacious with IFN-β, the current wariness over combination therapy will prove difficult for laquinimod to overcome. Thus, the drug will likely be used only as a

monotherapy. Teva anticipates filing with the FDA in 2011, and we expect laquinimod to launch in 2012 in the United States and Europe; peak-year sales will be in the range of $100-250 million.

Simvastatin

Simvastatin (Merck's Zocor) was launched in Europe in 1989 and in the United States and Japan in 1991 for the treatment of dyslipidemia. Owing to results of a preliminary open-label study investigating the efficacy of simvastatin in MS, it is the statin most likely to enter Phase III trials for this indication in the United States.

Simvastatin is structurally similar to the cholesterol precursor HMG-CoA and acts as a competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. Statins slow the production of cholesterol in the body and increase the liver's ability to remove low-density-lipoprotein (LDL, or "bad cholesterol") from the blood; statins, however, are commonly acknowledged to confer additional beneficial effects independently of their cholesterol-lowering activities. Termed *pleiotropic effects,* these actions stem from statins' ability to modify endothelial function, possibly by promoting the production of nitric oxide and inhibiting the production of inflammatory molecules in the endothelium (Wassmann S, 2001). Statins have multiple immunomodulatory effects; it has been suggested that they change the cytokine profile of T cells from the proinflammatory T_H1 profile to the anti-inflammatory T_H2 profile (Youssef S, 2002). Statins inhibit proteins essential for leukocyte infiltration into the CNS (notably the T-cell-associated integrin LFA-1 and MMP-9) and should reduce inflammation in MS patients, thereby slowing disease progression. In in vitro studies, statins inhibited the release of proinflammatory cytokines in leukocytes obtained from MS patients; simvastatin inhibited this release to a greater extent than other statins (e.g., lovastatin). The statins did induce the release of two proinflammatory cytokines known to play a role in MS: IL-12 and IFN-γ. The combination of IFN-β and statins reduced proinflammatory cytokine release in vitro to a greater extent than either agent alone, suggesting potential for combination treatment.

A small, multicenter, open-label study in 28 patients with RR-MS demonstrated that simvastatin significantly reduced the Gd-enhancing lesion load as assessed by MRI (Vollmer T, 2004). Daily doses of 80 mg simvastatin significantly reduced the number of Gd-enhancing lesions (by 44%) and their total volume (by 41%) over a six-month period.

Despite the encouraging results on the number and volume of Gd-enhancing lesions, simvastatin did not appear to have an effect on disease progression. Indeed, secondary end points assessing clinical progression of the disease did not reveal any effect of the drug on relapse rates or changes in EDSS score from baseline.

The results of the study are too preliminary to gauge whether statins will be used for the treatment of MS during our forecast period. The trial was small and was conducted over a short time frame; furthermore, it had an open-label design. Therefore, because patient lesion load at six months was compared with a baseline level instead of a placebo group, it is hard to determine

whether the reduction in active lesions seen in the study was due to the drug or simply to a natural remission of patients' exacerbations. The addition of a placebo-treated cohort in larger studies will help researchers distinguish between these two possibilities.

Simvastatin appeared to have no effect on the study's immunological end points, which should have been affected by the drug's postulated immunomodulatory actions. However, recent data have demonstrated that simvastatin has this capability. Simvastatin inhibited the activation of T cells and the expression of the proinflammatory T_H1 profile. The drug also inhibited the release of the pro-inflammatory cytokines IFN-γ, TNF-α, and IL-2 (Peng X, 2006). This finding, as well as its demonstrated positive effect on lesion number and volume, suggests that further examination of simvastatin as a potential treatment for RR-MS is warranted.

Because the significance of MRI lesion load on disease progression is still a matter of debate, larger studies will be needed to determine if statins have a disease-modifying effect on MS progression. Furthermore, larger studies will help determine an optimal therapeutic dose, which statin is most effective, whether adverse side effects appear with long-term treatment, and whether the optimal therapy is statin monotherapy or combination therapy with currently used disease-modifying drugs.

Statins offer important advantages over the current immunomodulating therapies: they are administered orally and well tolerated, and their cost is low. One caveat to consider in using statins for the treatment of MS is that the long-term side effects of chronic statin use are unknown; some reports associate kidney and liver damage with chronic statin use. In addition, because interferon therapy may also cause liver toxicity, the combination of statins and interferons may require caution and monitoring of liver function. Nevertheless, because statins offer clear advantages (oral administration, generally well tolerated, low cost), we will follow Phase III studies on statin therapy with interest.

Experts interviewed are interested in simvastatin as an MS therapy because, as one Spanish neurologist says simply, "It's oral and it could be efficacious for MS." A German neurologist adds, "From the mechanism of action, [simvastatin] might be [useful], but the doses are very high, and with this drug I'm very concerned about side effects." The majority of experts are concerned about side effects, particularly myopathy and rhabdomyolysis (a breakdown of muscle fibers that then are released into the blood and can lead to kidney damage)--muscle-related injuries that have been associated with statin use. Experts state that more trials are needed to study the efficacy and safety of simvastatin. However, despite the side effects, statins still hold potential as an MS treatment. As one neurologist states, "Statins will have their certain small niche. I have a lot of people who have failed everything and, for want of anything better, I've put them on a statin." Because simvastatin lost patent protection in 2006 in the United States and has lost protection in Europe, pharmaceutical companies will likely not fund large Phase III studies, so the clinical development of statins for MS will be slow. Because clinical studies to determine the potential benefit of statin therapy on

MS disease progression are still in early stages, we cannot forecast peak-year sales for simvastatin in this indication at this time.

Oral Immunosuppressants

Overview

Compounds in this class have been launched for cancer indications, but their broad immunosuppressant properties have been found useful in the treatment of aggressive forms of RR-MS and SP-MS and in MS refractory to interferon or glatiramer acetate treatment. Because the side effects of immunosuppressants are more severe than those of immunomodulators (particularly, the risk of opportunistic infections), their use is limited to aggressive forms of MS. Sanofi-Aventis, Teva/Merck Serono, and Wyeth have oral immunosuppressants in development for MS. Wyeth's temsirolimus is an analogue of sirolimus (rapamycin); the compound inhibits molecular target of rapamycin (mTOR), an enzyme that is critical for cell growth and proliferation. Thus, the drug interferes with T-cell proliferation; as an MS therapy, it will dampen the autoimmune response of myelin protein-specific T cells. Temsirolimus was in Phase II trials for MS as of March 2004, but no subsequent development has been reported. The drug remains in development for various cancers; temsirolimus received fast-track status from the FDA in March 2002 for its use in renal cell carcinoma, and in October 2006, the European Medicines Agency (EMEA)'s Committee for Medicinal Products for Human Use (CHMP) granted temsirolimus orphan drug status for mantle-cell lymphoma. Given the apparent slowdown in temsirolimus development for MS, we do not profile it here. In this section, we profile Sanofi-Aventis's teriflunomide and Merck Serono's cladribine (Mylinax), the most advanced oral immunosuppressants in development for the treatment of MS.

Mechanism of Action

Immunosuppressants function via a variety of mechanisms. In general, these agents exert their effects by blocking the activation and proliferation of activated T cells, thereby promoting the accumulation of anti-inflammatory molecules and reducing the formation of antibodies. Antiproliferative drugs often interfere with DNA and RNA synthesis in dividing cells; this mechanism of action targets very actively dividing cells such as cancerous cells and, in the case of MS, activated T cells. However, immunosuppressants also affect healthy, dividing cells, an action that explains the toxicity associated with this drug class.

Teriflunomide

Sanofi-Aventis's teriflunomide (HMR-1726) is a general oral immunosuppressive and antiproliferative agent being investigated for the treatment of MS. Teriflunomide is the active metabolite of leflunomide (Sanofi-Aventis's Arava), an immunosuppressant indicated for the treatment of RA. The drug entered Phase III trials in the United States for MS in February 2004, but data have not yet been released. Sanofi-Aventis is investigating teriflunomide in RR-MS patients and SP-MS patients experiencing relapses. Even though the company has not revealed whether the RR-MS patients have an aggressive form of MS, we expect that, because

teriflunomide is an immunosuppressant, the company would seek approval for worsening RR-MS or SP-MS patients who suffer relapses. The company announced at an information meeting in February 2007 that a second Phase III trial, expected to begin in June 2007, will investigate teriflunomide for early-stage MS and that a Phase II trial to begin in the second half of 2007 will assess the safety of teriflunomide in combination with either IFN-β or glatiramer acetate, although details of these studies have not been announced.

Teriflunomide blocks the proliferation of activated T cells by inhibiting the synthesis of pyrimidine, one of the four chemical building blocks of DNA and RNA. Specifically, teriflunomide inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in pyrimidine synthesis (Fox RI, 1998). Because the activated T cell is unable to synthesize a copy of its DNA necessary to complete cell division, the T cell cannot proliferate, and the inflammatory reaction is reduced. Teriflunomide may also inhibit lymphocyte tyrosine kinases and reduce T-cell responsiveness to IL-2. Unfortunately, because teriflunomide also affects healthy cells, its side effects are severe.

Sanofi-Aventis initiated a second Phase III trial in September 2004 to examine the efficacy of two doses of teriflunomide in patients with RR-MS and SP-MS with relapses. The randomized, double-blind, placebo-controlled study is slated to enroll 1,080 patients in Canada, the Russian Federation, and Europe. The study was expected to last for two years, followed by an open-label extension period of unspecified length. The primary end point is disability progression as assessed by EDSS score every 12 weeks; this end point is unusual as a primary end point (a drug's effect on relapse rate is a more common primary end point). However, should teriflunomide show efficacy on this end point, the company would benefit from a significant commercial advantage because few drugs have managed to demonstrate an effect on disability progression; thought leaders consistently note that a drug's effect on disability is the most relevant, desirable, and influential end point to achieve. Secondary end points of this study include frequency of relapses, burden of disease as measured by MRI, and safety. As of January 2007, the trial was continuing to enroll patients.

Results of a Phase II trial indicate that teriflunomide has efficacy similar to that of interferons and glatiramer acetate, as assessed by MRI (O'Connor PW, 2006). In a randomized, placebo-controlled trial, RR-MS patients were treated with 7 mg of teriflunomide (n=60), 14 mg of teriflunomide (n=56), or placebo (n=61) daily for nine months. The primary end point was the number of active lesions as assessed by MRI; secondary end points included relapse frequency and disease progression (as measured by EDSS). Teriflunomide treatment (both doses) reduced the number of active lesions by 61% compared with placebo, as well as the number of T1-enhancing and new or enlarging T2 lesions. Annual relapse rates declined by 32% with 14 mg teriflunomide treatment, a decline that was not significantly different from placebo. The higher dose of teriflunomide also significantly slowed disability progression, by 69%, at 36 weeks.

Teriflunomide was generally well tolerated, and the incidence of adverse events did not differ significantly among treatment groups. Nasopharyngitis, headache, and upper respiratory tract infections were the most commonly

reported effects across all treatment groups. Serious adverse effects, including hepatotoxicity, neutropenia, neuralgia, and rhabdomyolysis, were reported in patients from all treatment groups (n=7 placebo-treated patients, n=5 of low-dose teriflunomide-treated patients, n=7 of high-dose teriflunomide-treated patients), but no deaths were reported.

Concerns exist regarding teriflunomide's side effects because of the side-effect profile of its parent compound, leflunomide, whose side effects include agranulocytosis and thrombocytopenia; therefore, monitoring blood counts is required. Leflunomide is also associated with hepatotoxicity and, like other immunosuppressants, with opportunistic infections. Sanofi-Aventis states that the safety and tolerability of teriflunomide are acceptable, but these claims must be borne out in Phase III trials.

Despite teriflunomide's promising Phase II data on reduced progression of disability, Sanofi-Aventis still must demonstrate that teriflunomide has a clear beneficial effect on disease progression. In addition, the drug must continue to demonstrate an acceptable safety profile if it is to be used for RR-MS, even if other treatment options for aggressive RR-MS have poor safety profiles. The drug has efficacy comparable to that of the interferons and glatiramer acetate as assessed by MRI, but not by relapse rates, so it is doubtful that teriflunomide will be an attractive therapeutic option for RR-MS patients, despite its oral formulation. Neurologists interviewed express some interest in this drug, but they have mixed opinions on the potential for severe side effects. According to one physician, "I think teriflunomide is a very convenient drug. It's not very difficult to use. And it's interesting because it's an oral drug. That is very important for MS patients. And the target, the action of this drug is very interesting. I think for the future it's probably a good opportunity for MS patients." Another neurologist disagrees: "I'd use it in desperation; nowhere else. Giving drugs this dangerous orally doesn't make them safe."

We forecast that teriflunomide will launch in 2011 in the United States and 2012 in Europe, but given teriflunomide's side effects, the inconvenience of blood monitoring, and its likely status as the third oral therapy to market, we do not believe the drug will fare well in the face of competition in the RR-MS indication. Although Sanofi-Aventis intends to run trials of teriflunomide in combination with IFN-β or glatiramer acetate, we believe that patients and neurologists will be unwilling to use a drug with a potentially poor safety profile (that would also require monitoring) at early stages of the disease; we therefore forecast that the drug will be used as a monotherapy for aggressive RR-MS behind Rebif, FTY-720, natalizumab, and oral cladribine. The drug will also be used in SP-MS patients who continue to relapse and who have failed IFN-β agents, FTY-720, and oral cladribine; teriflunomide will compete with natalizumab, daclizumab, MBP-8298, and mitoxantrone in this patient population. However, because of its premium pricing (the drug was priced for its first launch in RA, a market that bears high pricing) and despite limited patient share, we expect that the drug will achieve peak-year, major-market sales in MS of $100-250 million.

Oral Cladribine

Cladribine (marketed by various subsidiaries of Johnson & Johnson and sold under the trademark Leustatin in the United States) was developed by Ortho Biotech (Johnson & Johnson) under license from the Scripps Research Institute and launched in February 1993 for the treatment of hairy-cell leukemia. Ortho was investigating the intravenous form of the drug for the treatment of MS, but the company withdrew a new drug application for MS in April 1999 (after an FDA warning about violations in its clinical studies), and Ortho returned its MS rights to Scripps. In December 2000, Ivax acquired the rights to the drug (renamed Mylinax) in MS. Ivax was conducting Phase III trials for the intravenous formulation of the drug in MS in November 2002. Ivax and Merck Serono entered an agreement in October 2002 to develop an oral formulation of cladribine for the treatment of MS with the aim of reducing the side effects of the injectable formulation. Results for Phase I trials were released in March 2004, and Phase II/III trials began in Canada in early 2005. Cladribine has orphan drug status for MS in the United States, and in September 2006, the drug received fast-track status from the FDA. Teva acquired Ivax in January 2006; according to a press conference held in September 2006, development of oral cladribine is being continued solely by Merck Serono, but Teva still stands to reap economic benefits if the drug is launched (Teva Pharmaceuticals: Innovative R&D Day transcript, September 26, 2006). Also, in January 2007, Merck KGaA completed its acquisition of Serono, renaming the company Merck Serono, and announced that enrollment in the pivotal Phase III trial has completed.

Cladribine is an analogue of deoxyadenosine, one of the building blocks of DNA and RNA. High levels of the drug accumulate in cells, enabling their incorporation into DNA and RNA molecules. Cladribine interferes with DNA polymerases (enzymes that duplicate novel DNA and RNA molecules) and thereby prevents the elongation of DNA strands that normally occurs during cell division and cell metabolism. As a result, cell death occurs, especially death of actively dividing cells. Activated T-cell and B-cell proliferation is the therapeutic target of low-dose cladribine in MS patients. The drug is delivered as an inactive precursor and requires activation by the enzyme deoxycytidine kinase; lymphocytes contain high levels of deoxycytidine kinase. As a result, the drug is particularly effective at inducing cell death in lymphocytes, thus reducing the immune response seen in MS patients.

A double-blind, placebo-controlled Phase III trial testing an oral formulation of cladribine began in Canada in early 2005 and has since been expanded to enroll patients in sites in the United States and Europe. End points of the Cladribine Tablets Treating MS Orally (CLARITY) trial include relapse rates, progression of disability, and MRI parameters. The trial is slated to last two years. Merck Serono completed enrollment of more than 1,300 patients in January 2007 and expects Phase III results in 2008.

Although the ongoing CLARITY trial will demonstrate whether oral cladribine is efficacious in RR-MS patients, Merck Serono and Teva have examined the efficacy of both oral and subcutaneous formulations of cladribine in RR-MS. Merck Serono and Teva announced positive results of a Phase I/II pharmacokinetic study for oral cladribine in March 2004.

Clinical and MRI end points were examined, although limited details of the trial's results are available. Double-blind, placebo-controlled Phase II trials examining the efficacy of a subcutaneous formulation of cladribine have led to contradictory results in RR-MS patients. The first trial, which enrolled 139 patients, demonstrated that 25 mg cladribine delivered subcutaneously each month for six montbs resulted in improvement in neurological function in 52% of treated patients (compared with 25% of placebo-treated patients) at 30 months (Grieb P, 1994). However, in the second trial, which enrolled 52 patients, patients treated with 0.35 mg/kg subcutaneous cladribine monthly for six months had a reduction in the frequency and severity of relapses and the number of enhancing MRI lesions, but the agent had no effect on relapse rate or neurological disability at 18 months (Romine JS, 1999). These results demonstrate that subcutaneous cladribine has potential efficacy in RR-MS, but large-scale trials of the oral formulation are required to determine its level of efficacy in this patient population. It appears that the positive data from the Phase I/II oral cladribine trial and the positive Phase II data using the subcutaneous formulation prompted the companies to continue development of oral cladribine in the large-scale Phase III trial.

Merck Serono initiated a two-year Phase II trial, the Oral Cladribine Added on to Rebif New Formulation in Patients with Active Relapsing Disease (ONWARD) trial, in January 2007 to assess the safety and efficacy of oral cladribine in combination with the reformulation of Rebif. The randomized, double-blind, placebo-controlled study will enroll 260 RR-MS patients who are currently taking Rebif but continue to relapse. Patients will receive one of two doses of oral cladribine administered as a four- or five-day pulse in combination with Rebif (44 mcg) administered subcutaneously three times weekly. The primary end points are the mean change in the number of Gd-enhancing lesions per patient, as assessed by MRI, and safety. With this trial, Merck Serono aims to position the drug as a safe and effective add-on therapy in RR-MS patients who are not sufficiently managed on Rebif alone.

Cladribine also shows mixed results in the CP-MS population, demonstrating an effect on relapses but not disability, suggesting that the drug would be useful only for SP-MS patients who continue to relapse. In a Phase III, placebo-controlled study involving SP-MS (70%) and PP-MS (30%) patients, cladribine caused more than 90% suppression of Gd-enhanced lesions but without a consequent improvement in EDSS scores (Rice GP, 2000). One-hundred-fifty-nine patients received a cumulative dose of cladribine of 0.7 or 2.1 mg/kg over the course of one year; patients' EDSS scores were assessed monthly, and lesions were evaluated biannually with an MRI scan. A subgroup analysis indicated that PP-MS patients experienced no reduction in the number of Gd-enhanced lesions or in their EDSS scores after cladribine treatment. However, the drug did have an effect on the number of lesions in SP-MS patients. The difference was still significant at two years in patients treated with the higher dose of cladribine. The EDSS scores of SP-MS patients treated with cladribine tended to stabilize compared with placebo-treated patients' scores; the investigators speculate that the results failed to reach significance because the placebo group fared unexpectedly well.

Cladribine appears to have a modest degree of efficacy in delaying the clinical worsening of SP-MS, but the drug is not as effective for RR-MS

and PP-MS; Phase II trials involving RR-MS patients have not convincingly demonstrated the drug's efficacy in this population. Consequently, we foresee this drug being used in patients with rapidly worsening RR-MS and in SP-MS patients who relapse. The drug has a less severe side-effect profile than that of mitoxantrone and is generally well tolerated. However, like mitoxantrone, it has a lifetime dose limit because it suppresses platelet production in bone marrow. Bone marrow toxicity is a side effect seen in leukemia patients treated with cladribine, but MS patients are treated with one-tenth the dose used in leukemia patients, and while platelet counts are affected, the effect is not severe enough to warrant treatment discontinuation, at least over the short time period of the Phase III trials (six months). Opportunistic infection (especially herpes zoster) is the most common side effect seen in treated patients. Other health risks may develop over the longer term; such concerns remain to be resolved in longer Phase III trials. The drug's oral formulation will give it a significant commercial advantage, mitigated by the likely requirement for blood monitoring.

Neurologists interviewed are divided in their opinions of cladribine; some are excited by the prospect of an oral formulation and the drug's efficacy, but most are withholding judgment until additional clinical trial data are available. "If oral cladribine keeps the same efficacy profile as the original drug formulation, I think it might be another option for patients," states one neurologist. Experts also express concern about the drug's long-lasting effects. Although the drug's long half-life provides it with a dosing advantage (twice yearly), experts warn that this same feature could be a safety concern because reversing the drug's effects quickly enough to address the infection may be impossible.

Should Merck Serono's oral cladribine prove efficacious in Phase II and III trials and overcome issues of variable bioavailability, we forecast that, given the drug's fast-track status designation, the drug will launch in early 2010 in the United States and Europe. We expect oral cladribine to be used in RR-MS patients who are deteriorating rapidly and in SP-MS patients; although we anticipate some use of the drug in SP-MS patients who are no longer relapsing, most of the SP-MS patients who receive this drug will be those experiencing relapses. Oral cladribine will be the first oral therapy to market, but we do not expect it to be used first-line because of concerns over safety and efficacy. The second-to-market oral MS agent, FTY-720, which will launch later in 2010, will compete with oral cladribine in both the aggressive RR-MS and the SP-MS indications.

Although Merck Serono's Phase II ONWARD trial is designed to assess oral cladribine as a potential combination therapy, experts interviewed remain leery of the prospect of combining immunomodulatory therapies because of the development of severe opportunistic infections (i.e., PML) observed in clinical trials investigating the natalizumab/Avonex combination. Experts interviewed state that long-term safety data beyond the standard two-year timeline would adequately address safety concerns and would encourage them to consider such a treatment regimen. However, cladribine delivered as a pulse should theoretically be safer than if the agent is administered chronically. Experts acknowledge that because autoimmune cells reconstitute slower than the normal immune system cells, patients who receive a pulse

of cladribine should benefit from a lower risk of opportunistic injections and should be free from the relapses caused by autoimmune cells. In the absence of robust safety and efficacy data, we forecast that oral cladribine will be used as a monotherapy because of physicians' negative opinion of combination therapy.

Estimating that patients with aggressive RR-MS or SP-MS represent 10% of drug-treated MS patients, we anticipate that cladribine could garner peak-year, U.S. and European sales of $100- 250 million for MS.

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MULTIPLE SCLEROSIS 2005-2020

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Chapter 7

Emerging Injectable Immunomodulatory Therapies

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.5401.2615 ♦ Fax +81.3.5401.2617

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7. Emerging Injectable Immunomodulatory Therapies

Key Findings

- The diversity in the mechanisms of action demonstrated by injectable immunomodulatory therapies in development for MS represents a wide-ranging effort to identify novel therapeutic candidates. However, whether any such agents will delay disease progression is unclear.
- PDL BioPharma/Biogen Idec's daclizumab will be the first agent to launch during our forecast period, but its use will be constrained by safety and efficacy concerns. The drug will be used predominantly in the CP-MS population but will also be used to treat aggressive RR-MS.
- BioMS Medical's altered peptide ligand MBP-8298 is targeted at the critically underserved CP-MS population, specifically the subset of patients who express the HLA-DR2 and HLA-DR4 alleles.
- Emerging therapies that launch for MS by 2020 will steal some market and patient share from current therapies, although current therapies will continue to dominate the market. The new agents will serve niche patient populations, including aggressive RR-MS, SP-MS, and refractory disease.

"We have already tried drugs, like cyclosporin, that are so effective on the immune system they can stop rejection of heart transplant. We can't stop MS with these drugs. So it tells us that the immune system may not be the primary problem. Yet more and more immunosuppressants are being developed. I think they're going to have about the same effect as present drugs."

—Neurologist, United States

Early-Stage Pipeline Status of Immunomodulatory Drugs by Class for Multiple Sclerosis, 2007

Key Classes	PC	I	II
Monoclonal antibodies	●	●	●●●●●●
Altered peptide ligands			●
Chemokine receptor antagonists	●●●●	●●	●
T-cell-receptor vaccines			●●
Peptide-encoding DNA plasmids			●
Nonoral immunomodulators	●●	●●●●●	●
Novel interferon betas	●●●●●	●	●
VLA-4 modulators		●●●	●
mTOR antagonists	●●●		
Cell-signaling modulators	●	●	
Other MS agents	●●●	●●●●	

● = one drug.

VLA = Very late antigen.

Note: Numbers reported here are Decision Resources estimates of key agents based on review of multiple publicly available databases and information.

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Overview

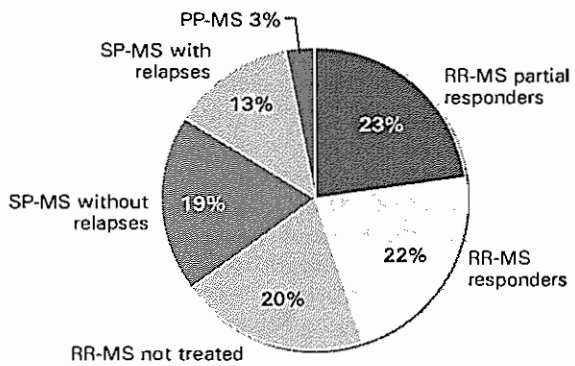
Despite advances in the treatment of multiple sclerosis (MS), significant unmet need remains because current therapies are effective in only 20-33% of all MS patients and 30-50% of relapsing-remitting (RR-MS) patients. The remaining RR-MS patients have only partially controlled disease progression, do not respond to the drugs, or remain untreated (see Figure 7-1). Patients with chronic-progressive forms of MS (CP-MS)—that is, secondary-progressive (SP-MS) or primary-progressive MS (PP-MS)—have limited or no therapeutic options, respectively.

Several compounds are being investigated in SP-MS and PP-MS patients. However, most of the clinical trials involve only a small number of patients, focus primarily on the SP-MS population that is still experiencing relapses (and therefore still have an immunological aspect to their disease), and often also include RR-MS patients, so it is not clear whether these compounds will remain in development for CP-MS. Most experts interviewed remain unconvinced that therapies now in development will prove efficacious in CP-MS patients, although they are cautiously optimistic that future treatments for this patient population will become available.

Most immunomodulators and immunosuppressants in development for MS have novel mechanisms of action compared with current therapies; the majority of these drugs are discussed at length in this chapter. Another immunosuppressive compound also in development for MS for which available information is limited and which is therefore not discussed in detail is Berlex's (the U.S. affiliate of Bayer Schering Pharma [formerly Schering]) fludarabine (Fludara), which is approved for refractory chronic lymphocytic leukemia. Berlex is developing fludarabine as an adjunct

Figure 7-1

Multiple Sclerosis Patient Populations, 2007



PP-MS = Primary-progressive multiple sclerosis; RR-MS = Relapsing-remitting multiple sclerosis; SP-MS = Secondary-progressive multiple sclerosis.

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therapy for RR-MS patients who experience relapses while on IFN-β therapy. The drug is a proapoptotic purine analogue that may inhibit lymphocyte proliferation during an autoimmune attack (relapse). A randomized, open-label Phase II study of 20 RR-MS patients on Avonex examined the safety, tolerability, and efficacy of three monthly cycles of fludarabine (25 mg/m^2, administered by IV daily for five days) compared with three monthly infusions of methylprednisolone (1 g administered once). Interim results presented in abstract form demonstrated a trend toward improved efficacy with fludarabine compared with methylprednisolone as measured by MRI, exacerbation frequencies, and clinical end points (18th Annual Meeting of the Consortium of Multiple Sclerosis Centers, June 2-6, 2004, Toronto). Fludarabine was well-tolerated; commonly reported adverse effects included transient neutropenia and fatigue. Despite the promising preliminary data, no further information on the developmental status of fludarabine is currently available.

Two other compounds that stalled in development but were of interest to experts because they were novel were Pfizer's interleukin-1β-converting enzyme (ICE, also known as caspase-1) inhibitors and Bayer's BAY-361677. Pfizer was conducting preclinical studies of ICE inhibitors for the potential treatment of several inflammatory disorders, including MS, Crohn's disease (CD), and rheumatoid arthritis (RA). The compounds appear to inhibit the release of proinflammatory cytokines. As of July 2006, no development had been reported in any indication. In addition, Bayer was developing the IL-4 agonist BAY-361677 as a potential treatment for MS. The compound was in Phase I trials for this indication and in preclinical development for acute lymphoblastic leukemia. However, in October 2006, development in both of these indications was terminated.

Emerging Injectable Immunomodulatory Therapies Positioning

Few injectable agents will launch for MS during our study period, and the agents that are slated to launch have thus far not demonstrated superior safety and equivalent or improved efficacy compared with that of current therapies. As a result, IFN-β (Bayer Schering Pharma's Betaferon/Berlex's Betaseron, Biogen Idec's Avonex, and Merck Serono [formerly Serono]/Pfizer's Rebif) and glatiramer acetate (Teva Pharmaceutical's Copaxone) will continue to dominate the market as the leading treatments for RR-MS during our study period. Emerging injectable agents will be used primarily to treat underserved patient populations, such as CP-MS patients, patients with aggressive RR-MS, and patients who do not respond to current therapies. These patient populations represent untapped market potential because they have few therapeutic options (for instance, SP-MS patients can be treated only with Betaseron, which is often not efficacious, or mitoxantrone [Merck Serono/Amgen's Novantrone], which can be taken only for two to three years because it has a lifetime dose limit owing to the drug's cardiotoxicity). Natalizumab (Biogen Idec/Elan's Tysabri), which is more efficacious than other current therapies but is hampered by severe side effects (progressive multifocal leukoencephalopathy [PML]), is often administered only to patients with aggressive RR-MS.

As a result of the cases of PML seen with the natalizumab/Avonex combination, a drug's safety profile has become paramount to its market success. Certain immunomodulatory agents in development that are profiled in this chapter have broad immunosuppressive properties, an attribute that raises concerns whether they carry the risk of severe opportunistic infections. Thought leaders speculate that the FDA is unlikely to accept applications for MS drugs without at least two years of data and will likely require postmarketing Phase IV surveillance programs to confirm a drug's side-effect profile. However, because of the high unmet need in MS, particularly in patients with aggressive RR-MS or CP-MS, we expect that the FDA will continue to afford priority reviews to promising agents even if those agents show less-favorable safety profiles.

Experts interviewed are skeptical that emerging immunomodulatory and immunosuppressive agents will achieve significant market success because they do not offer improvements in safety and efficacy over that of current therapies. In addition, their formulations (injections or infusions) fail to afford a commercial advantage over existing therapies. However, most experts acknowledge that these agents will provide therapeutic options to underserved niche populations, including CP-MS patients and patients with aggressive RR-MS.

None of the immunomodulators in clinical development for the treatment of MS are designed to cure the disease, but several drugs—such as the monoclonal antibodies (MAbs) rituximab (Biogen Idec/Genentech's Rituxan) and daclizumab (Roche's Zenapax; being developed for MS by PDL BioPharma and Biogen Idec)—may be able to prevent further disease progression. Other drugs, such as the altered peptide ligand MBP-8298, offer limited therapeutic advantages to specific patient subgroups, notably the critically underserved CP-MS population.

Keys to success for emerging injectable therapies include an increase in overall drug-treatment rates (including the treatment of aggressive RR-MS, CP-MS, and MS patients who have abandoned therapy) and stealing patient share from current therapies because of increased efficacy in those niche populations.

Immunomodulatory drug development in MS is focusing predominantly on MAbs and chemokine receptor antagonists, although many other agents in development have other mechanisms of action. This variety in the pipeline is an indication of researchers' lack of understanding about which mechanisms of action will provide the greatest therapeutic benefit in MS. Drug companies are no longer vigorously pursuing VLA-4 antagonists because of concerns that the agents' mechanism of action may lead to opportunistic infections (see Chapter 2, "Current and Emerging Drug Targets"). Figure 7-2 summarizes non-oral drugs in early phases of development, and Figure 7-3 outlines non-oral drugs in late stages of development for MS.

Table 7-1 lists the injectable immunomodulatory drugs in development for MS profiled in this chapter.

Figure 7-2

Early-Stage Pipeline Status of Injectable Immunomodulatory Drugs by Class for Multiple Sclerosis

Key Classes	PC	I	II
Monoclonal antibodies	●	●	●●●●●●
Altered peptide ligands			●
Chemokine receptor antagonists	●●	●●	●
T-cell receptor vaccines			●●
Peptide-encoding DNA plasmids			●
Novel interferon betas			●
VLA-4 antagonists			●

● = one drug;

VLA = Very late antigen.

Note: Numbers reported here are Decision Resources estimates of key agents covered in this report based on review of multiple publicly available databases and information.

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Monoclonal Antibodies

Overview

Several MAbs have reached clinical trials for MS: daclizumab, alemtuzumab (Genzyme/Bayer Schering Pharma's Campath), and rituximab (Biogen Idec/ Genzyme's Rituxan).

Other MAbs are in earlier stages of development for MS. Acorda Therapeutics' M1 MAbs (a mix of naturally occurring MAbs against undisclosed spinal cord proteins) are still in discovery phase to promote remyelination in rodent models of MS. Clinical trials are under way for other MAbs, including Abbott/Cambridge Antibody Technology's ABT-

Figure 7-3

Late-Stage Pipeline Status of Injectable Immunomodulatory Drugs by Class for Multiple Sclerosis

Key Classes	III	PR/R	MKT
Interferon betas			●●●
Altered peptide ligands	●		●
VLA-4 antagonists			●

● = one drug.

VLA = Very late antigen.

Note: Numbers reported here are Decision Resources estimates of key agents covered in this report based on review of multiple publicly available databases and information.

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Table 7-1

Emerging Injectable Immunomodulatory Therapies in Development for Multiple Sclerosis, 2007

Compound	Status	Marketing Company	Peak-Year Sales Potential[a] ($MM)
Monoclonal antibodies			
Rituximab (Rituxan/MabThera)[b]			No launch expected
United States	II and II/III[c]	Biogen Idec/Genentech	
Europe	—	Roche	
Japan	—[d]	—	
Daclizumab[e]			100-250
United States	II	PDL BioPharma /Biogen Idec	
Europe	II	PDL BioPharma /Biogen Idec	
Japan	—	—	
Alemtuzumab (Campath/Mabcampath)[f]			No launch expected
United States	II	Genzyme/ Bayer Schering Pharma	
Europe	II	Genzyme/Bayer Schering Pharma	
Japan	—	—	
Altered peptide ligands			
MBP-8298			250-500
United States	II[h]	BioMS Medical	
Europe	II and II/III[i]	BioMS Medical	
Japan	—	—	
Chemokine receptor antagonists			
MLN-1202			No launch expected
United States	—	Millennium Pharmaceuticals	
Europe	II	—	
Japan	—	—	
T-cell receptor vaccines			
NeuroVax			Lack of data precludes estimate
United States	II	Immune Response	
Europe	—	—	
Japan	—	—	
Tovaxin			No launch expected
United States	II	Opexa Therapeutics	
Europe	—	—	
Japan	—	—	
Peptide-encoding DNA plasmids			
BHT-3009			Lack of data precludes estimate
United States	II	Bayhill Therapeutics	
Europe	II	Bayhill Therapeutics	
Japan	—	—	

(continued)

Table 7-1 (cont.)

Emerging Injectable Immunomodulatory Therapies in Development for Multiple Sclerosis, 2007

a. Represents peak-year sales in the major pharmaceutical markets for the indication under study only. Methodology is explained in the "Emerging Injectable Immunomodulatory Therapies" chapter of the text.
b. Marketed for B-cell non-Hodgkin's lymphoma.
c. Rituximab is in Phase II for relapsing-remitting MS and in Phase III for primary progressive MS.
d. Roche (formerly Chugai) currently markets rituximab in Japan for B-cell lymphoma. However, there does not appear to be any ongoing development for rituximab in Japan for multiple sclerosis.
e. Marketed for control of kidney transplant rejection.
f. Marketed for chronic lymphocytic leukemia.
g. Schering is being acquired by Bayer and was renamed Bayer Schering Pharma in December 2006.
h. Trials are being conducted in Canada.
i. MBP-8298 is in Phase II trials for relapsing-remitting MS and Phase II/III for primary progressive MS.

Note: Status is based on databases such as R&D Insight and the Investigational Drugs Database (IDdb); periodicals such as Scrip, the FDC's Pink Sheet, and Marketletter; company reports and press releases; and industry contacts.

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874, Bristol-Myers Squibb's CTLA4-Ig (abatacept, Orencia), MacroGenics' MGA-031, and Centocor's CNTO-1275, but limited information is available about their progress.

Abbott Laboratories is developing ABT-874 under license from Cambridge Antibody Technology as a potential treatment in MS, psoriasis, CD, and RA. ABT-874 is a MAb directed against the proinflammatory cytokine IL-12. Abbott initiated a randomized, placebo-controlled Phase II study in MS patients in June 2004 to examine the efficacy of weekly or biweekly ABT-874 compared with placebo. The trial was expected to last 48 weeks—a 24-week placebo-controlled phase followed by a 24-week open-label extension phase—and will evaluate the drug's ability to reduce the number of Gd-enhancing lesions as assessed by MRI. Experts caution that because ABT-874's mechanism of action inhibits only one of the several proinflammatory cytokines secreted by activated T cells, the agent's efficacy may be low. Should the drug's side-effect profile prove safe and the drug reach the market, we expect it to be used for RR-MS and perhaps SP-MS with relapses because it targets the inflammatory response in MS patients. However, because we do not expect the drug to be efficacious in all MS patients, it will likely be administered only to patients who have failed to respond to the IFN-βs and glatiramer acetate. Results of the Phase II trial were expected in 2006, but no information was available as of early 2007.

Bristol-Myers Squibb is developing CTLA4-Ig for multiple autoimmune indications. The drug was launched in the United States for RA in February 2006; CTLA4-Ig is also preregistered in Europe for RA and in Phase II trials in Japan for the same indication. CTLA4-Ig is an antagonist of the T-cell coreceptor molecule CD28; inhibition of CD28 prevents activation of T cells as well as production of proinflammatory cytokines. CTLA4-Ig was in Phase II trials for MS in January 2003; as of February 2007, the drug continued to be in development for MS, although no data have been published thus far. As of September 2005, the drug was also in Phase IIb trials for systemic lupus

erythematosus (SLE). Neurologists interviewed are generally skeptical of the drug because it targets only one aspect of the immune response, T-cell activation, but most agree that it should be tested for MS.

MacroGenics is developing MGA-031 (teplizumab, hOKT3γ1-Ala-Ala) for a number of autoimmune diseases, including MS, type 1 diabetes, and psoriatic arthritis. MGA-031 binds to one chain (ε) of CD3, part of the T-cell-receptor complex expressed on T cells, thus interfering with the antigen recognition process. MacroGenics acquired this compound from Tolerance Therapeutics. The FDA granted MGA-031 orphan drug status for recent-onset type 1 diabetes in October 2006; Phase II/III trials for this indication are planned. A Phase I trial for MS was slated to begin in 2006 in collaboration with the National Institutes of Health, but no announcement of this trial's initiation had been made as of early 2007.

Centocor is developing a MAb against IL-12 and IL-23 for potential treatment of MS, psoriasis, and CD. A Phase I trial of CNTO-1275 for RR-MS was initiated in 2002; data were presented at the ECTRIMS meeting in September 2004. This double-blind, placebo-controlled, dose-escalation study examined lesion volume and number in 20 RR-MS patients treated with one of four doses of CNTO-1275 (0.3, 0.75, 1.5, 3.0 mg/kg, administered subcutaneously one time). Lesion number and volume in CNTO-1275-treated patients were not different from placebo at any dose tested. The drug was generally well tolerated, although one serious adverse effect was reported (i.e., malignant breast tumor). A Phase II double-blind, placebo-controlled, dose-escalation study was initiated in July 2004; the 250 RR-MS patients enrolled in the study received one of three doses (30, 100, 200 mg) subcutaneously eight times over the 23-week study period. End points of this study include the number of new Gd-enhancing lesions as assessed by MRI, relapse number, and changes in EDSS. The drug remains in development for psoriasis and CD.

In the following section, we focus our discussion on daclizumab, alemtuzumab, and rituximab for the treatment of MS.

Mechanism of Action

Most MAbs under development target the inflammatory phase of MS. Instead of suppressing the entire immune system, like standard immunosuppressant therapy, MAbs offer the promise of suppressing specific steps in the cascade of events leading to inflammation in MS, thereby providing potentially more-tolerable therapy. Activated T cells, for instance, are major players in the inflammatory phase of MS, and several MAb-based therapeutic strategies seek to prevent T-cell activation or to suppress activated T cells. T cells can be suppressed in several ways. For example, daclizumab, alemtuzumab, rituximab, and CTLA4-Ig are highly specific antibodies that bind to target proteins (antigens) on the surfaces of lymphocytes (T cells and B cells), thus preventing their activation and proliferation and the subsequent development of inflammation in MS.

Rituximab

Biogen Idec and Genentech are developing rituximab as a potential treatment for MS. The drug is marketed by these companies as Rituxan in the United States and by Roche as MabThera outside the United States for the treatment of relapsed or refractory, low-grade, CD20-positive, B-cell non-Hodgkin's lymphoma and for RA in the United States. Roche (formerly Chugai) markets rituximab in Japan for B-cell lymphoma, but no development has been reported in Japan for other indications. Rituximab has completed Phase II trials in the United States in RR-MS patients, but neurologists interviewed are especially excited about the ongoing Phase II/III trial for PP-MS because no therapeutic option exists for this patient population. In addition, rituximab was approved by the FDA in February 2006 for the treatment of RA and in September 2006 for use in two additional forms of non-Hodgkin's lymphoma. Rituximab is being evaluated across a range of other immunological indications, including vasculitis and SLE.

Rituximab is a mouse/human chimeric MAb that targets CD20, a protein found on the surface of B lymphocytes. Once marked with the anti-CD20 antibody, the body's natural immune defenses are recruited and attack and kill the marked B cells, thereby leading to B-cell depletion. Recent evidence that some forms of MS have a B-cell component lends credence to rituximab's mechanism of action and efficacy in some patients (Archelos JJ, 2000; Kieseier BC, 2005). For instance, in patients with PP-MS or SP-MS, the level of MBP-specific antibodies secreted by B cells in the brain and cerebrospinal fluid (CSF) is substantially increased and is associated with the severity of myelin destruction (Warren KG, 1986; Warren KG, 1987). Thus, destroying B cells may improve clinical outcomes in these patient populations. Indeed, one case study showed that rituximab depleted B cells in an RR-MS patient with a very aggressive course of the disease; the patient had no relapses during treatment, remained relapse-free for nine months, improved on EDSS (from 6 to 4), and did not form any new Gd-enhancing lesion after six months of treatment. In addition, a small-scale, non-placebo-controlled study demonstrated that four doses of 375 mg/mm^2 rituximab in four patients with neuromyelitis optica (NMO; Devic's disease) rendered B-cell counts undetectable after the second infusion; this state was maintained at six months (Cree BA, 2005). Seven of eight patients experienced improvement in neurological function; average EDSS scores improved from 7.5 at baseline to 5.5 during treatment. Six of the eight patients in this study remained relapse-free at 12 months.

In August 2006, Genentech and Biogen Idec announced the results of the Phase II trial to evaluate the safety and efficacy of rituximab in RR-MS patients. The randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of rituximab in 104 RR-MS patients. The primary end point was the total number of Gd-enhancing lesions compared with placebo as assessed by MRI at 12, 16, 20, and 24 weeks. At each of these time points, rituximab-treated patients showed a statistically significant reduction in the number of Gd-enhancing lesions. Overall rates of adverse effects were comparable between the two groups.

Severe adverse reactions are associated with rituximab—namely up to 77% incidence of first-infusion reactions as a result of a severe cytokine release, which has led to eight fatalities since 1998. Rituximab therefore carries a black box warning for potentially fatal infusion reactions on its product label. The labeling for rituximab indicates that the drug is associated with other serious adverse events, including tumor lysis syndrome, mucocutaneous reactions, cardiac arrhythmias and angina, and renal failure. Results from the Phase II RR-MS trial showed that rituximab-treated patients had increased rates of nasopharyngitis, upper respiratory tract infections, sinusitis, and urinary tract infections compared with placebo-treated patients, as well as greater incidence of severe infections (gastroenteritis and bronchitis). A greater number of first-infusion reactions were reported with rituximab treatment compared with placebo, but none of the reactions were severe or fatal. Some physicians report that the long-term safety of rituximab as a chronic therapy is a significant concern. According to one neurologist, "Rituximab has interesting data in Phase II from Genentech, but, again, a program that cuts down such a wide swath of immune cells as all the CD20 B cells has got to be dangerous in the long run." Adds another neurologist, "Unfortunately, the only way to know what's going to happen is with time. The more patients who are treated, the longer time goes, and if, eventually, it is shown that monotherapy was the way to go, then we are going to be fine. But, again, we need more patients and more time for follow-up."

Neurologists interviewed by Decision Resources are interested in the initiation of a double-blind, placebo-controlled Phase II/III trial for rituximab in the PP-MS population, for which no therapy is currently available. The drug has anecdotally shown efficacy in PP-MS, but no data have been published to support this claim. Enrollment in this trial began in June 2004 and was completed at the end of 2005, a remarkably fast enrollment that underscores the huge unmet need in this patient population. The trial enrolled 435 patients and will evaluate the time to confirmed disease progression over 96 weeks of treatment as a primary end point. Safety and tolerability of the drug are other primary end points. Secondary end points will evaluate the efficacy of rituximab compared with placebo in this patient population. Results are expected in 2008.

The emergence of rituximab as a treatment for MS has evoked considerable interest among neurologists interviewed despite concerns about safety. The possibility of a therapeutic option for PP-MS would revolutionize MS treatment and ensure rapid uptake of the agent, despite its potential safety risks, because of the relentless progression of disability that characterizes this form of MS. However, not all experts are convinced that rituximab or other MAbs will be effective MS treatments. As one expert states, "Monoclonal antibodies may look very good, but I find it impossible to believe that a single monoclonal treatment can be as effective as anything in all groups of patients."

Rituximab appears to be well tolerated in cancer and RA patients thus far; however, given the paucity of clinical data regarding its efficacy in PP-MS, we are unable to speculate as to rituximab's promise in Phase III trials. The potential for efficacy cannot be gleaned from small Phase II studies in RR-MS because RR-MS and PP-MS have fundamentally different pathologies

(and may in fact be different diseases) and no drug efficacious in RR-MS has proved efficacious in PP-MS to date. Similarly, gauging a drug's safety based on results seen in other autoimmune diseases, such as RA, is risky because MS patients can react very negatively to drugs commonly used in other autoimmune indications (e.g., TNF-α inhibitors) (Robinson WH, 2001). Therefore, in the absence of reliable safety and efficacy data from large trials, we cannot predict that rituximab will prove efficacious in the treatment of MS, so we are unable to forecast its launch in this indication.

Daclizumab

Daclizumab was launched in the United States (1997) and Europe (1999) as Roche's Zenapax for control of kidney transplant rejection. PDL BioPharma (formerly Protein Design Labs), the original developer of the drug, is studying the drug in MS and indications other than transplant and respiratory diseases (i.e., uveitis and type 1 diabetes) in collaboration with Biogen Idec. In August 2006, PDL BioPharma announced that Roche is discontinuing its role in the development of daclizumab in asthma, and in November 2006, the companies announced a discontinuation of their collaboration to develop this drug for transplant maintenance; PDL BioPharma indicated that it will need a partner to continue development of daclizumab for asthma. Daclizumab is in Phase II development in the United States for RR-MS and SP-MS patients who have failed IFN-β therapy and who have aggressive forms of MS. PDL BioPharma completed a small, open-label, pilot Phase II trial of daclizumab in MS in April 2004; the company is conducting a larger Phase II trial that is enrolling 270 RR-MS patients and is expected to be completed in April 2007.

Daclizumab is a humanized MAb directed against the alpha subunit of the interleukin-2 (IL-2) receptor on activated T-helper cells and prevents IL-2 from binding to this receptor. Because IL-2 stimulates T cells to divide, daclizumab suppresses an immune response by inhibiting the proliferation of activated T-helper cells.

The drug shows efficacy as a monotherapy in patients who have failed first-line treatments, particularly in SP-MS patients, a patient population that has proved hard to treat. A small open-label Phase II trial that enrolled 7 RR-MS patients and 14 SP-MS patients with EDSS scores of 2.5-6.5 showed encouraging results (Rose J, 2004a; Rose J, 2004b). Prior to daclizumab treatment, 17 of these patients had failed IFN-β therapy and 2 were untreated; the patients had aggressive forms of MS as assessed by MRI and clinical features (i.e., EDSS scores). Patients received monthly doses of 0.8-1.9 mg/kg daclizumab as a monotherapy or in combination with IFN-β. The average length of treatment was 13.6 months for all patients; one patient discontinued therapy because of discomfort in the hands, and one patient discontinued therapy because of a severe attack coinciding with initiation of therapy. Ten patients experienced an improvement of 1.0-4.5 points on the EDSS, sustained over at least 14 months; five of these ten patients had SP-MS. In addition, nine patients in the study stabilized as measured by a reduction of 0.5 points or less in their EDSS scores; significantly, eight of these patients had SP-MS. Overall, the mean EDSS score of patients at the study's end was 4.02 points, a significant reduction ($p<0.001$) over the mean baseline score of 5.47. Treatment with daclizumab caused a significant reduction in the

percentage of scans with active lesions. At the end of the trial, 15% of scans showed evidence of active lesions versus 39% at baseline. The annualized relapse rate for all patients fell from 1.23 at baseline to 0.32 during treatment.

Overall, treatment with daelizumab was well tolerated, although one patient developed an infection—an expected risk, caution experts interviewed, in a drug targeting IL-2 signaling. Six patients experienced abnormal touch sensation, such as burning or prickling (paresthesia), which resolved with continued treatment. Mild leukopenia was observed in one patient, a transient, low-level increase in liver enzymes was noted in another, and a mild rash developed in four patients, but these effects did not cause these patients to drop out. Spasms were also reported in one patient.

PDL BioPharma and Biogen Idec are further evaluating the safety and efficacy of daclizumab in a randomized, double-blinded, placebo-controlled Phase II trial, the CHOICE trial, which is slated to enroll 270 patients with aggressive RR-MS. Two doses of daclizumab delivered subcutaneously will be tested as adjunct therapy to IFN-β treatment. The study's primary outcomes include the number of new or enlarged active lesions (Gd-enhancing) on monthly brain MRIs collected over the course of 24 weeks. Secondary outcomes include clinical improvement and immunogenicity. Biogen Idec announced that enrollment was completed in the first quarter of 2006 and results are expected in early 2007 (Biogen Idec First Quarter 2006 Earnings Conference Call, April 26, 2006). This trial is being conducted based on encouraging data from an earlier small, open-label Phase II trial that found that daclizumab (1 mg/kg delivered at two-week intervals for the first two doses and then at four-week intervals, for a total of seven infusions) showed efficacy as an add-on therapy in patients with either very active RR-MS or SP-MS; daclizumab reduced the number of total and new brain lesions (by 70% and 78%, respectively) and the number of exacerbations (by 81%), although it had only a slight benefit on clinical disability (Bielekova B, 2004).

PDL BioPharma and Biogen Idec are also enrolling 264 RR-MS patients in a Phase II trial of three doses of daclizumab as a monotherapy. Primary end points include the number of Gd-enhancing lesions and the number and volume of new T2 lesions. Secondary end points include relapse rate, incidence of antibody formation to daclizumab, and overall safety and tolerability. Results are expected in 2008.

Although most physicians interviewed expect daclizumab to demonstrate clinical efficacy, they are not convinced that its mechanism of action will translate into superior clinical efficacy over current therapies because the drug inhibits the signaling of only one cytokine, IL-2. In addition, some experts interviewed by Decision Resources are leery of severe long-term side effects, including the risk of developing opportunistic infections, leukemia, and anaphylaxis.

The companies are positioning daclizumab for use in patients who have not responded to first-line immunomodulatory therapies: patients with aggressive forms of RR-MS and patients with relapsing SP-MS. These patients have limited therapeutic options, so the side-effect profile of a drug that shows

efficacy in those patient populations can be less favorable than that of a first-line therapy. Currently, the most efficacious therapeutic option for SP-MS patients and patients with aggressive forms of RR-MS who have failed IFN-β treatment is mitoxantrone, a chemotherapeutic agent with significant toxicity; by comparison, daclizumab appears to be well tolerated. However, the IFN-βs and glatiramer acetate are better tolerated and do not carry the opportunistic infection risk, so daclizumab will have to prove safe in Phase III trials before the companies can expand the drug's indication to first-line therapy for RR-MS.

To compete in the MS market as a monotherapy, daclizumab must demonstrate at least equal efficacy to the IFN-βs in preventing or delaying disease activity and progression. Alternatively, the drug must provide significantly increased efficacy in combination with the IFN-βs over IFN-β monotherapy if it is to be used as an adjunct to IFN-β therapy.

Daclizumab's main competitor will be natalizumab, and Biogen Idec and PDL BioPharma will likely position daclizumab for a different patient population than that of natalizumab to avoid product cannibalization—we expect that daclizumab will launch in the United States in 2009 and Europe in 2010, three years after natalizumab's reapproval in the United States and four years after its launch in Europe. Alternatively, Biogen Idec may consider daclizumab to be a less efficacious but safer therapeutic option than natalizumab, and it may position daclizumab as first-line therapy, before natalizumab and mitoxantrone, in patients with aggressive RR-MS and patients who are not responding to traditional first-line therapies. We believe that even if daclizumab maintains a favorable safety profile, it is unlikely to outperform natalizumab in the MS market because of its inferior efficacy. Assuming that less than 5% of the drug-treated MS population will receive daclizumab, we forecast peak-year sales for MS in the range of $100-250 million.

Alemtuzumab

Alemtuzumab (Berlex/Ilex Oncology's Campath and Bayer Schering Pharma/Ilex Oncology's Mabcampath) is a MAb originally developed at Cambridge University in the United Kingdom. A joint venture was formed between Ilex Oncology and Millennium Pharmaceuticals (formerly LeukoSite) in 1997 to develop this drug. In 1999, Millennium and Ilex granted Schering and its U.S. affiliate Berlex exclusive marketing and distribution rights to alemtuzumab for the treatment of chronic lymphocytic leukemia (CLL) and other indications in the United States, Europe, and the rest of the world, excluding Japan and East Asia; in February 2003, Schering's marketing rights were expanded to include Japan and East Asia. In December 2001, Ilex gained sole ownership of the partnership by acquiring Millennium's interests in the alemtuzumab joint venture; Ilex was then acquired by Genzyme in December 2004. Alemtuzumab was launched in 2001 in the United States and Europe as a third-line therapy for the treatment of B-cell CLL. The drug is also in development for MS, hematological malignancies, and non-Hodgkin's lymphoma.

Alemtuzumab is a seleetive humanized MAb direeted against CD52, a glyeosylphosphatidylinositol-anehored glyeoprotein of unknown function expressed on all mature lymphoeytes and monocytes. Beeause alemtuzumab is speeific for CD52, it can deplete the disease-causing activated lymphocytes but will spare lymphocyte precursors, which express CD52 only later in development. Binding of the MAb to the cell surface initiates a cascade of events culminating in cell death. By targeting and depleting lymphocytes (and inflammatory T cells in particular), developers hope that the agent will halt or slow the inflammatory process that characterizes MS.

The companies initiated a Phase II trial in December 2002 in the United States and Europe to compare the efficacy of alemtuzumab (infusion of 60 mg and 120 mg once yearly) with that of Rebif (44 mcg). The three-year, randomized, open-label Phase II study enrolled 334 patients with early, active RR-MS (RR-MS of less than three years' duration and EDSS lower than 3.5). Primary end points included relapse rates and the time to progression of disability as measured by the EDSS.

Interim data reported in a September 2006 press release showed that at two years, alemtuzumab had efficacy superior to that of Rebif but was associated with significant side effects, notably idiopathic thrombocytopenic purpura (ITP), a drop in blood platelet counts. Patients treated with alemtuzumab showed a greater than 75% reduction in the risk of relapses over that of Rebif, and a reduction in the risk of disability progression by at least 65%. The companies also reported that secondary effieacy end points, including MRI and functional assessments, demonstrated alemtuzumab's greater efficacy compared with Rebif's, although details of these results are lacking.

Although the interim data from this Phase II trial yielded positive efficacy results for alemtuzumab, the trial was suspended by Bayer Schering Pharma and Genzyme in September 2005 because three patients developed ITP, and one case proved fatal. Two of the three ITP cases were in patients treated with high doses of alemtuzumab. Genzyme has since established a risk management program (submitted to the FDA in February 2006) and implemented extensive monitoring for ITP. Three additional patients were identified with ITP symptoms, and all responded well to medical treatment.

This trial demonstrated that alemtuzumab is also associated with other serious adverse effects. Although specific information about these side effects is lacking, adverse events were reported in eight alemtuzumab-treated patients (four on each dose) and two patients receiving Rebif. Incidents of thyroid-related effects occurred in 11% of alemtuzumab-treated patients, compared with 1.9% of Rebif-treated patients. The most commonly reported side effects were infusion reactions in alemtuzumab-treated patients and flulike symptoms in Rebif-treated patients. However, because of the cases of ITP, the trial remains on hold until regulatory agencies can complete safety and risk management assessments.

According to a Septeinber 14, 2006, Genzyme press release, Bayer Schering Pharma and Genzyme plan to initiate a Phase III trial in the first half of 2007, and the companies are working with both the FDA and EMEA in designing and implementing this trial. The companies have announced that they will

use lower doses in this trial. Until the clinical hold is lifted on the Phase II trial, the Phase III trial will not commence.

Initially, researchers thought alemtuzumab would be most appropriate for patients with chronic-progressive forms of MS (i.e., PP-MS and SP-MS), but clinical trials did not support this hypothesis. In a Phase II trial of 29 SP-MS patients with EDSS scores between 4.0 and 6.0, investigators measured the effect of a single infusion of alemtuzumab after 18 months by MRI end points including MRI assessment of the number and volume of Gd-enhanced lesions and hypointense lesion volume on a T1-weighted sequence (Paolillo A, 1999). Because hypointensity on an unenhanced T1 sequence is seen in approximately 20-30% of chronic MS lesions, the researchers theorized that it most likely indicates an important degree of axonal loss. Additionally, they measured spinal cord atrophy with serial MRI imaging and cerebral atrophy with brain extraction performed on Gd-enhanced, T1-weighted imaging. Patients treated with alemtuzumab (n=25) experienced a significant reduction in the number and volume of Gd-enhancing lesions, compared with the untreated control group (n=4), indicating suppression of active inflammation.

Despite this positive finding, approximately 50% of patients had progressive disability, as measured on the EDSS, increasing brain atrophy because of axonal degeneration, and increasing spinal cord atrophy at the end of 18 months. Many patients developed increasing T1 hypointensity. Alemtuzumab treatment produced rapid lymphopenia, but the extent of lymphopenia did not correlate with suppression of disease activity visible on MRI (Paolillo A, 1999).

Evidence of alemtuzumab's poor safety profile was shown in a follow-up to the Phase II study conducted by A. Paolillo and colleagues (Coles AJ, 1999). In this study, one-third of the patients treated with alemtuzumab developed Graves' disease, an autoimmune disease in which the immune system produces immunoglobulins (antibodies) that target and stimulate the thyroid gland. It is the leading cause of hyperthyroidism. The incidence of Graves' disease in untreated MS patients and patients treated with Betaseron is 1-2%. In more than 600 patients treated with alemtuzumab for various other disorders, there have been no reports of Graves' disease; this finding suggests that patients with MS are uniquely susceptible to this complication (Coles AJ, 1999). Experts interviewed for this report warn against the long-term side effects of depleting mature lymphocytes; possible side effects include the risk of developing hematologic toxicities (pancytopenia, thrombocytopenia) and opportunistic infections. Other side effects reported in alemtuzumab patients include secondary infections, fevers, chills, nausea, and vomiting.

Despite the encouraging Phase II results, the vast majority of physicians interviewed are greatly concerned about alemtuzumab's side-effect profile. Alemtuzumab's efficacy will have to prove significant enough (i.e., better than that of currently available treatments) in Phase III trials to justify the risk of developing Graves' disease or ITP. Graves' disease, a permanent, albeit treatable, disorder, is especially troublesome to treating physicians and their patients because the average patient with RR-MS is young. ITP is also treatable, but it must be detected before it becomes irreversible. Although the risk of Graves' disease was lower in this study than in other studies, the

incidents of ITP have negatively affected this drug's future, likely dashing Bayer Schering Pharma and Genzyme's hopes of positioning alemtuzumab as a competitor to IFN-β. Experts' concerns over the side-effect profile will discourage use of alemtuzumab because of the requirement for blood and thyroid monitoring and the severity of potential side effects. Instead, the drug may be repositioned for RR-MS patients who have failed IFN-β therapy. However, physicians will likely use natalizumab or mitoxantrone before alemtuzumab despite their risks because these drugs have shown therapeutic efficacy and slightly better safety profiles, leaving alemtuzumab unable to compete even in the niche population of early aggressive RR-MS. Alemtuzumab's superior efficacy over Rebif and its convenient once-yearly dosing will likely be insufficient to offset physicians' concerns about ITP and Graves' disease. In addition, the fact that clinical trials continue to be on hold does not bode well for the drug's future. Even though Bayer Schering Pharma and Genzyme are working closely with regulatory agencies before resuming clinical trials, we do not expect the companies to pursue the development of alemtuzumab for MS based on physicians' apprehension about the drug's side-effect profile (in a market sensitized to side effects by natalizumab's unexpected safety risks).

Altered Peptide Ligands

Overview

Altered peptide ligands (APLs) in development include BioMS Medical's MBP-8298 and Teva's TV-5010. MBP-8298 is composed of a single peptide ligand templated on the natural sequence of the myelin basic protein (MBP); it is unlike the currently available APL glatiramer acetate (Teva's Copaxone), which is a mixture of several peptide ligands based on the natural sequence of the MBP. TV-5010 is a copolymer composed of the same four amino acids as glatiramer acetate. Its exact formulation and mechanism of action are not clear, but the drug is believed to have an immunomodulatory effect. Phase II trials examining the safety and efficacy of TV-5010 in RR-MS patients are ongoing, and the compound is in development for CD, amyotrophic lateral sclerosis, Huntington's disease, and glaucoma, although clinical trial data are lacking. Emerging APLs will play only a minor role in the MS market because data suggest they are effective only in subgroups of patients and because they have the potential for serious side effects. However, MBP-8298 shows promise because it appears effective in SP-MS, a patient population with few therapeutic options.

Experts interviewed are aware of the potential of APLs for MS treatment, but they emphasize the high degree of uncertainty about these agents' efficacy. They cite the complexity and diversity of human T-cell response to CNS candidate autoantigens and note that APLs will be effective only if they can be individualized or tailored to individual patients or groups of patients with similar immunological features. Patients with the *HLA-DR2* or *-DR4* gene appear to be responders to MBP-8298. Therefore, by enriching the trial population with this responder patient population, BioMS Medical may have been able to detect a therapeutic effect whereas previous drug development programs (e.g., Neurocrine Biosciences' tiplimotide) failed to demonstrate efficacy of a similar APL in the RR-MS population at large.

Mechanism of Action

APLs, also known as peptide analogues, have minor substitutions in their amino acid sequences compared with the natural peptide. Although APLs' exact mechanism of action remains unclear, several hypotheses have been advanced to explain their efficacy. When administered to patients with MS, APLs bind to the same T-cell receptor (TCR) as the original peptide that initiated the pathological immune responses in MS and in doing so alter the pathological immune response. Although they can bind to the TCR, APLs cannot activate T cells because the costimulatory signal necessary to activate T cells can be given only if a peptide is presented by an antigen-presenting cell (APC). Because APLs bind directly to the TCR without involving an APC, no costimulatory signal is delivered to the T cell and it is not activated; this unactivated state is known as "anergy."

APLs may also function as partial agonists: APLs binding to TCRs would activate only a subset of T-cell-signaling events. For instance, T cells bound with APLs would secrete cytokines but would fail to proliferate (Duda PW, 2000a; Genain CP, 2000).

A third possible mechanism of action of APLs is their ability to change the cytokine profile of disease-causing T cells in animal models (Windhagen A, 1995). For instance, APLs may induce inactivated T cells to become T_H2 cells (which secrete anti-inflammatory cytokines) instead of T_H1 cells (which secrete proinflammatory cytokines), a phenomenon known as "immune deviation" (Duda PW, 2000b; Kappos L, 2000). This deviation would also downregulate other proinflammatory T_H1 cells, regardless of their antigenic specificity, in a process known as "bystander suppression." Researchers have demonstrated bystander suppression by showing that in mice injected with two different, disease-causing T-cell lines, subsequent administration of an APL for one cell line blocked the disease-producing capabilities of both lines. This finding is significant because it indicates that APLs, in targeting some of the more common antigens (MBP, for example), could affect other, as-yet-unidentified disease-causing antigens. Because MS is believed to be caused by heterogenic immune cells, successful APL therapy, researchers theorize, would require these agents to act on more than a single immunological process.

MBP-8298

Development of MBP-8298 began at Rycor Technology Investments, under license from the University of Alberta. In August 2001, BioMS Medical (formerly EPS Capital) acquired all outstanding shares of Rycor and an exclusive worldwide license to MBP-8298 patent claims for the treatment of MS. BioMS Medical has long-term manufacturing agreements with UCB-Bioproducts and Hospira Worldwide for MBP-8298. BioMS Medical is developing MBP-8298 to treat patients suffering from CP-MS (SP-MS and PP-MS). Enrollment in a Phase II/III trial in SP-MS patients began in December 2004 in Canada and has been expanded to include several European countries, including Germany, Spain, and the United Kingdom; the company announced the completion of patient enrollment in January 2007. BioMS Medical also initiated a Phase II trial in RR-MS patients in August 2006, and, in January 2007, the company received FDA approval to initiate

a Phase III trial in the United States. BioMS Medical has been seeking a development partner for the agent since late 2002.

MBP-8298 is a synthetic peptide derived from natural MBP, the principal protein present in myelin, which inhibits the production of antibodies to endogenous MBP. The peptide is designed to mimic the portion of MBP most frequently recognized by T cells in MS patients (Martin R, 1991). In patients with PP-MS or SP-MS, the level of MBP-specific T cells and MBP-specific antibodies secreted by B cells in the brain and CSF is substantially increased and is associated with the severity of myelin destruction (Warren KG, 1986; Warren KG, 1987). Although the drug's mechanism of action is still unclear, experts speculate that MBP-8298 acts by preventing activation of T cells by binding to the TCR and preventing these T cells from being activated by natural MBP peptides presented via an APC; as a result, these T cells enter a state of anergy.

MBP-8298 also acts by antagonizing MBP-specific antibodies secreted by activated B cells. Under normal conditions, an activated T cell will in turn activate B cells to differentiate; differentiated B cells secrete antibodies that damage cells via the complement cascade (by boring holes in the membrane of a cell, notably the cells that produce myelin). By preventing myelin-specific T cells from becoming activated, MBP-8298 prevents B-cell activation and subsequent cell damage from the complement cascade. Finally, MBP-8298 can bind to MBP-specific antibodies secreted by differentiated B cells and thus prevent myelin damage caused by the complement cascade. BioMS Medical researchers theorize that if MBP-8298 can suppress specific MBP autoantibodies associated with MS demyelination, further demyelination can be prevented and disease progression halted or delayed.

Clinical trials of MBP-8298 have focused on a specific population of MS patients, based not only on the disease subtype (CP-MS) but also on the expression of a particular subset of genes. The *HLA-DR2* and *HLA-DR4* genes are major histocompatibility complex (MHC) class II alleles (also called human leukocyte antigen [HLA] alleles) and are the genes most consistently implicated in genetic risk of MS (Noseworthy JH, 2000). The proteins encoded by these genes are associated with the activation of T-helper cells, which in turn are involved in the activation of B cells producing anti-MBP antibodies. Experts interviewed estimate that this genetic background is present in 50-75% of the MS population—the *HLA-DR2* gene appears to contribute between 15% and 60% genetic susceptibility in MS (Oksenberg JR, 2005a) .

Following receipt of FDA clearance in January 2007, BioMS Medical plans to initiate a Phase III trial in the United States. The randomized, double-blind, placebo-controlled study is slated to enroll 510 SP-MS patients who will receive MBP-8298 intravenously once every six months for two years. Approximately 75% of the patients are expected to carry the *HLA-DR2* or *-DR4* allele. The primary end point of this study is the time to disease progression, as measured by EDSS.

A Phase II/III double-blind, placebo-controlled trial to examine the efficacy of MBP-8298 in CP-MS is slated to include approximately 550 patients

who will receive MBP-8298 as an infusion once every six months for two years; it is one of the few trials for an emerging therapy in MS studying a chronic-progressive patient population. The trial will include a minimum of 408 patients who carry the *HLA-DR2* or *HLA-DR4* gene. The trial will also include at least 100 patients who do not carry either gene. The study's primary end point is the time to progression of the disease as assessed by the EDSS. The secondary end point is disease progression in patients who do not carry the *HLA-DR2* or *HLA-DR4* gene. Enrollment was completed in January 2007; interim data are expected in mid 2008.

Phase II investigations suggest that MBP-8298 is very effective at slowing disease progression in the subgroup of CP-MS patients who carry either the *HLA-DR2* or *HLA-DR4* gene. BioMS Medical conducted a four-year Phase II trial in 32 patients with either PP-MS or SP-MS; the patients with either of the key genes were distributed evenly between the MBP-8298 group (n=10) and the placebo group (n=10). The study had two phases: a two-year, placebo-controlled, randomized, double-blind phase, in which patients were given 500 mg of MBP-8298 or placebo intravenously every six months, followed by a two-year, open-label phase. Data were analyzed for the overall population and for the genetic subgroup of patients who carried either the *HLA-DR2* or *-DR4* gene. BioMS Medical conducted this subgroup analysis to determine whether the company can more accurately identify potential responders to its therapy.

The study's primary end point was disease progression; results from this trial suggested that fewer MBP-8298-treated patients with the *HLA-DR2* and *HLA-DR4* alleles deteriorated compared with patients with other HLA alleles (Warren KG, 2006). Patients were considered to have deteriorated elinically if they had a confirmed change in EDSS of greater than or equal to 1.0 when their baseline scores were less than or equal to 5.0, or a change of greater than or equal to 0.5 when their baseline scores were greater than or equal to 5.5. Five of the 16 patients treated with MBP-8298 deteriorated during the double-blind phase, compared with 9 of the 16 patients on placebo, a difference that was not statistically significant. However, significantly fewer MBP-8298-treated patients with the *HLA-DR2* or *HLA-DR4* gene deteriorated (0%) than placebo-treated patients with the *DR2/4* genes (60%) at the end of the double-blind phase at two years. At the end of the open-label phase (the four-year mark), 30% of the *HLA-DR2* or *HLA-DR4* MBP-8298-treated patients had deteriorated on EDSS. The drug was generally well tolerated in this study: no serious adverse events were observed in treated patients, and no difference in the frequency of adverse events was seen between treated patients and placebo.

The trial also identified MS patients who showed complete or partial suppression of anti-MBP antibodies following injections of MBP-8298 and determined whether this suppression correlated with any clinical stabilization (Warren KG, 2006). Investigators measured anti-MBP antibody levels in patients' CSF. In the blinded phase, *HLA-DR2* or *HLA-DR4* patients who were treated with MBP-8298 showed a significant and sustained reduction in anti-MBP antibodies that was significantly related to the absence of deterioration as measured by EDSS. These data support an earlier Phase I study in 56 CP-MS patients in which 25 of the 41 MBP-8298-treated

patients (61%) demonstrated anti-MBP suppression into the normal range as measured by CSF antibody levels (Warren KG, 2000). In the placebo group, autoantibody levels were found to be elevated in all 15 patients throughout the two-year trial. No clinically relevant side effects were observed in this trial.

Significantly, MBP-8298 appears to delay the progression of disease in CP-MS patients (Warren KG, 2006). Long-term follow-up data demonstrated that MBP-8298 delays disease progression for five years. This five-year, open-label, follow-on study to a Phase II study was conducted in 20 progressive MS patients and found that MBP-8298 delayed the median progression of MS by 78 months (6.5 years) in patients treated with MBP-8298 compared 18 months (1.5 years) with patients who were treated with placebo during the original closed phase of the study. No serious adverse effects were reported during the follow-up period; the most commonly reported side effect was injection-site redness and burning.

Although BioMS Medical is focusing on development of MBP-8298 for CP-MS, the company is actively expanding MBP-8298's indications to RR-MS patients. A Phase II trial was initiated in Europe in August 2006 to evaluate the efficacy of MBP-8298 in RR-MS patients, and the first patients were enrolled in November 2006. The 12-month, double-blind, placebo-controlled study is expected to enroll 215 patients who express the *HLA-DR2* or *HLA-DR4* alleles. The double-blind phase will be followed by a 15-month open-label extension phase. End points include relapse rate, disease progression, and disease activity as measured by MRI.

MBP-8298 appears to have a good safety profile thus far: injection-site irritation is the most prevalent side effect. Because the drug's mechanism of action is so specific, the risk of opportunistic infections seen with less-specific immunosuppressants (e.g., chemotherapeutics) will likely not be as much of a concern with MBP-8298 because the majority of the patient's immune system is left intact. Nineteen of 32 patients in the Phase II study have been treated for seven years, suggesting that the drug is safe when administered chronically; however, only 32 patients have been treated in the Phase II study thus far. In August 2006, BioMS Medical announced its intention to conduct an interim safety and efficacy analysis of the first 200 patients enrolled in the Phase II/III study once those patients completed two years of the study; at that time, more than 300 patients had already enrolled in the trial. The results of this interim analysis will be critical for assessing the long-term safety of MBP-8298.

Most physicians interviewed are not familiar with MBP-8298, and experts' reactions are mostly negative concerning the use of *HLA-DR* alleles to identify responders to MBP-8298. Although some experts assert that *HLA-DR* alleles may hold some benefit in directing drug design, most physicians interviewed do not anticipate widespread screening for *HLA-DR* alleles, and simple diagnostic tests are not readily available. One expert explains, "*HLA-DR2,* for instance, is associated with MS but is not expressed by all individuals with MS. At least 50% of patients are *-DR2*-negative, so this wouldn't be a valid approach to diagnosing MS." Yet, about 50% of MS

patients express the *HLA-DR2* or *-DR4* alleles, representing a large patient population that may benefit from MBP-8298.

BioMS Medical intends to position its drug first for SP-MS patients. The SP-MS patient population is attractive because it represents the approximately 25% of the MS population with few therapeutic options. The high unmet need in the SP-MS patient population and the dearth of drugs in the pipeline for this patient population provide a significant commercial advantage to MBP-8298. The only drugs currently approved for this patient population are Betaseron (for SP-MS patients in the United States who are relapsing—approximately 40% of the SP-MS population) and the immunosuppressant mitoxantrone (which has a poor safety profile and a lifetime dose limit that is typically reached in two to three years). MBP-8298's impressive efficacy in patients carrying the *HLA-DR2* or *-DR4* gene and its benign side-effect profile make it likely that MBP-8298 will perform well in this market niche. Furthermore, its administration schedule (once every six months) is one of the most convenient in the MS market.

The number of MS patients with either the *HLA-DR2* or *HLA-DR4* gene is still not clear. According to experts interviewed and genetic studies, the percentage of patients carrying these genes may represent 50-75% of the MS population, so the drug may be effective in 10-20% of the total MS population (Oksenberg JR, 2005a). Should the drug continue to prove effective and safe, it could see significant uptake in this niche population. We expect the drug to launch in 2011 in the United States and Europe and garner peak-year, major-market sales of $250-500 million for the treatment of SP-MS and RR-MS patients with the *HLA-DR2* or *-DR4* gene.

Chemokine Receptor Antagonists

Overview

Chemokines are small proteins that guide circulating leukocytes to sites of inflammation by binding to receptors on the surface of leukocytes; they have been implicated in a variety of inflammatory disorders and autoimmune diseases. For nearly 30 years, researchers have been testing the theory that antagonizing chemokine receptors could prevent the passage of leukocytes into the brain, thus preventing inflammation and halting the progression of MS. Chemokine receptors are subdivided into ten families, and leukocytes bearing a wide variety of chemokine receptors have been identified in MS patients. The two receptors that have been the focus in clinical development for MS are the cell-cycle regulatory-1 (CCR1) and CCR2 receptors (Charo IF, 2006).

However, the cases of PML in patients treated with natalizumab have underscored the risks associated with preventing leukocyte trafficking through the BBB. Because leukocytes carry a variety of different chemokine receptors, the risk inherent in targeting these proteins may be mitigated if the specific chemokine receptors present on autoimmune activated T cells are identified and targeted; however, this specificity has proved elusive thus far (Charo IF, 2006).

Several companies, including Millennium Pharmaceuticals, ChemoCentryx, and Advanced Immuni T, are vigorously pursuing chemokine receptors as targets for MS. Millennium's pipeline includes MLN-1202, an antagonist against the CCR2 receptor, which we profile later in this section. Millennium and Sanofi-Aventis have formed a collaborative CCR1 receptor antagonist program for the treatment of RA and MS; MLN-3897 (AVE-9897) is the lead compound in this program. Sanofi-Aventis continues to list the drug in Phase I trials for MS, although no development has been reported in this indication as of March 2007. Millennium appears to be reprioritizing MLN-3897 for RA, and the compound is in Phase II trials for this indication. MLN-3897's oral availability will provide a significant commercial advantage should the drug launch.

Another inhibitor of the CCR2 receptor, CCX-915, is in development by ChemoCentryx as an oral treatment for MS. ChemoCentryx filed an NDA with the FDA in November 2005 and is conducting Phase I clinical trials to examine the safety and tolerability of CCX-915; the study was expected to be completed in 2006 but had not as of early 2007. Although CCX-915 is in development primarily for MS, it will also be investigated in other indications, including RA and atherosclerosis.

Advanced Immuni T is developing Peptide T, a synthetic peptide segment of a protein component of the HIV envelope, for multiple autoimmune disorders, including MS, Alzheimer's disease (AD), IBD, CD, and HIV/AIDS. Peptide T inhibits a different chemokine receptor, CCR5, than other chemokine receptor antagonists in development, but like other compounds in this drug class, it promotes expression of anti-inflammatory cytokines, which will act to suppress the inflammatory response in MS. As of August 2004, the compound was in Phase I/II clinical trials for MS. No additional information on its developmental status for MS is available.

Other companies have been pursing chemokine receptor antagonists as potential MS treatments, but these companies have disclosed little information about their programs and some appear to be progressively testing these agents for RA instead of MS. Pfizer has a CCR2 inhibitor research program under license from Incyte, and Pharmacopeia Drug Discovery has a CCR1 antagonist research program. Anormed reportedly had a CCR1 inhibitor program, but the company was acquired by Genzyme in 2006 and this program appears to have been discontinued. ChemoCentryx has a CCR1 antagonist research program, but the company is focusing on the treatment of RA. Merck was developing a CCR2 receptor antagonist, MK-0812, which was in Phase II trials for RR-MS in August 2004 but is no longer listed as in development. Because it is the chemokine receptor antagonist furthest along in development, we focus our discussion on MLN-1202.

Mechanism of Action

Chemokines are molecules that attract monocytes and activated T cells from the circulatory system, across the BBB, and into the CNS of MS patients. They are secreted by macrophages in early demyelinating plaques in the CNS of MS patients (Sunnemark D, 2003). Chemokines bind a family of CCR receptor proteins that are expressed on the cell surface of leukocytes;

each receptor binds specific cytokines. Several members of the CCR family, including CCR1 and CCR2, are expressed on the surface of monocytes and activated T cells. Once the chemokines have bound to the CCR receptor, they instruct T cells and monocytes to follow increasing concentrations of the chemokines until the T cells reach the demyelinating plaques in the CNS of MS patients. Chemokine receptor antagonists prevent cytokines from binding the CCR receptor, thereby interrupting the chemokine signal that attracts the immune system cells into the CNS of MS patients.

MLN-1202

Millennium's chemokine receptor antagonist MLN-1202, a humanized antibody targeting the CCR2 receptor, is in development for MS, atherosclerosis, and scleroderma. MLN-1202 is in Phase II trials for MS as of June 2005; results are expected in the first half of 2007. The agent was also in development for RA, but the company announced in January 2006 that it was not moving forward with development for this indication.

MLN-1202 is designed to block the CCR2 receptor and prevent the infiltration of a subset of leukocytes—macrophages and monocytes--into the brain where they will release proinflammatory cytokines and elicit myelin and neuronal damage. The primary ligand for the CCR2 receptor is the monocyte chemoattractant protein-1 (MCP-1), which has been implicated in RR-MS patients and animal models of MS (Mahad DJ, 2003; Sorensen TL, 2004).

In June 2005, Millennium initiated a Phase II trial testing the safety and tolerability of multiple doses of MLN-1202 in 40 RR-MS patients. Patients were treated for four months with MLN-1202 administered as an intravenous infusion. The trial is also evaluating the effect of the drug on disease activity as assessed by MRI parameters.

Most experts agree that if MLN-1202 launches, the drug will not prove more efficacious than other disease-modifying drugs and will most likely be used as an adjunct to disease-modifying therapy for RR-MS, a regimen experts expect will offer modestly greater benefits than disease-modifying monotherapy. Experts interviewed are guarded in their enthusiasm for this mechanism of action and raise concerns about the drug class's efficacy and potential side effects. Some physicians are concerned that chemokine receptor antagonists' general immunosuppressive effects may impair patients' immune responses to infectious disease (Eliecs MJ, 2002; Gao JL, 1997; Gerard C, 1997), but most physicians are indifferent about this drug class, citing the similar immunomodulatory properties of existing therapies and other drugs in development.

MLN-1202's efficacy may suffer from the same problem plaguing other members of its class: redundancy of the chemokine system. Because other chemokine receptors may compensate for the loss of CCR2, antagonizing one chemokine receptor may not produce significant clinical effects (Wiendl H, 2003). This compensation is likely the cause of poor Phase II efficacy results seen with BX-471, a CCR1 antagonist that was in development by Berlex, and is the reason we are not hopeful regarding the success of MLN-1202. More worrisome is the possibility that opportunistic infections will develop

if macrophages are prevented from passing through the BBB. Depending on the pathogen, if an opportunistic infection occurs in the brain, T cells cannot be activated because MLN-1202 will prevent macrophages from crossing the BBB and presenting foreign antigens to T cells in the brain; without this antigen presentation, T cells will not be activated and will not be able to combat the infection in the brain. Therefore, the possibility of opportunistic infection persists with a CCR2 receptor antagonist. It is possible, however, that microglia, which can act as APCs in the CNS, would preclude the risk of opportunistic infection, thus significantly improving the drug's safety profile.

As an intravenously administered antibody, MLN-1202 does not have the advantage of convenient oral administration that small-molecule inhibitors in this drug class have. Because of the redundancy intrinsic in the chemokine receptor family, we forecast that the drug will show only modest efficacy, even in larger-scale trials. Given the poor efficacy results seen with Berlex's now defunct BX-471 (due to redundancy in the chemokine receptor family), the possibility of a poor safety profile, and the injectable formulation—all of which fail to distinguish MLN-1202 from its competitors—as well as physicians' lack of interest in this drug class, we do not expect the drug to launch for the treatment of MS.

T-Cell Receptor Vaccines

Overview

Several T-cell receptor vaccine programs were in development for the treatment of MS, including programs at Aixlie, ImmuLogic (in collaboration with Bayer Schering Pharma), and Connectics. All were discontinued in preclinical phases of development (except the Connectics program, discontinued in Phase II) so that the companies could refocus their efforts on more-promising compounds. In 1999, Connectics sold the rights to its program to Immune Response, which is developing the T-cell receptor vaccine NeuroVax. Opexa Therapeutics is developing the MS vaccine Tovaxin. We discuss both NeuroVax and Tovaxin in the following sections.

Mechanism of Action

The T-cell receptor vaccine targets a receptor on autoimmune T cells, the T cells that most frequently attack the myelin sheath in MS patients. The strategy aims to activate a class of T cells known as "regulatory T cells," which will then specifically downregulate or delete the autoimmune T-helper cells involved in the breakdown of myelin in MS patients.

NeuroVax

In 1999, Immune Response bought the rights to the T-cell receptor vaccine from Connectics and, in November 2000, began Phase I/II trials. The company discontinued the program in September 2002 so that it could focus its efforts on developing its core product, Remune. Immune Response announced in February 2006 that it would focus its strategy on NeuroVax and was planning trials to assess the drug's effect on MS relapse rates and disability. The company initiated a Phase II trial in RR-MS and SP-MS patients in March 2005; results were presented at the 58th American

Academy of Neurology meeting in San Diego in April 2006. The company subsequently initiated a larger Phase II trial in RR-MS patients in March 2007. In addition, Immune Response initiated discussions with potential partners for Phase III development and commercialization of NeuroVax in April 2006.

NeuroVax is a combination vaccine (an incomplete Freund's adjuvant) of three peptides that are identical to the T-cell receptors of three T cells (that recognize MBP) found in high levels in the CSF or the plaques of MS patients. These pathogenic T cells are believed to be involved in the breakdown of the myelin sheath in these patients. The vaccine is expected to elicit an immune response by activating regulatory T cells, which can downregulate the pathogenic T_H1 cells involved in the breakdown of myelin while leaving normal T cells unaffected. The adjuvant in which the three peptides are dissolved is necessary to induce an immune response because, in the absence of the adjuvant, the immune system tolerates these peptides, as it does the natural T-cell receptors found on the pathogenic T cells. Recent studies have shown that levels of regulatory T cells are reduced in MS patients compared with healthy individuals. Regulatory T cells expressing the forkhead (FOXP3) transcription factor are thought to mediate self-tolerance—that is, they are responsible for preventing the activation of T cells recognizing self-antigens. NeuroVax appears to increase levels of FOXP3-positive regulatory T cells in RR-MS patients, which would restore self-tolerance in these patients.

The Phase II trial is evaluating the safety and efficacy of NeuroVax in 200 RR-MS patients in eastern Europe. This multicenter, randomized, double-blind, placebo-controlled study will enroll patients with EDSS scores of 5.5 or lower. Patients will receive either NeuroVax (100 mcg/mL of each of the three TCR peptides) or placebo. The primary end point is the number of new Gd-enhancing lesions as assessed by MRI at 24, 32, 40, and 48 weeks. Secondary end points include analysis of clinical relapses and neurological disability at 12, 24, 36, and 48 weeks, immunologic measurements, and safety. The study is slated to last for 48 weeks, and results are expected in 2008.

In March 2005, Immune Response initiated a small Phase II trial to examine the efficacy of NeuroVax in SP-MS. The open-label study enrolled 40 patients with RR-MS or SP-MS; 30 of these patients were enrolled in previous NeuroVax trials. Patients will receive NeuroVax injections once monthly for three months, followed by injections each quarter for three quarters. Results are expected in early 2007.

Immune Response presented data in abstract form suggesting that NeuroVax increased the number of T cells responsible for inducing immune tolerance, including T cells that secrete the cytokine IL-10 and regulatory T cells that express the *FOXP3* gene (regulatory T cells). Data were presented at the 21st Congress of the European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS) in Thessaloniki, Greece, in October 2005 (Vandenbark A, 2005) and at the 58th American Academy of Neurology meeting. After three monthly injections of NeuroVax, the number of T cells secreting IL-10 and the number of regulatory T cells expressing the *FOXP3*

gene were increased in treated RR-MS patients compared with their baseline, suggesting that the immune system was altered to become tolerant of the myelin antigens present in the vaccine. NeuroVax also induced a strong immune response in a subgroup of six MS patients after 48 weeks. This patient group had increased their levels of regulatory T cells to the same level seen in controls. These positive results were seen after one year of treatment with NeuroVax: levels of regulatory T cells were increased in 14 out of 17 patients treated with monthly injections of NeuroVax over the course of one year, as measured by increased *FOXP3* mRNA and protein levels in these patients. Thus, immune reactions against the natural proteins in the brain could theoretically be reduced. The study was very small and open-label; a beneficial clinical effect of this enhanced self-tolerance will have to be demonstrated in the Phase II trial that began enrollment at the end of 2006.

Although data on immunogenicity and increased self-tolerance appear encouraging, in that most patients develop an immune response against the vaccine, data on the depletion of pathogenic T cells and consequent clinical stabilization of the disease are still lacking. Earlier Phase I/II data presented in abstract form at the 56th Annual Meeting of the Academy of Neurology in San Francisco suggest that the vaccine does affect the clinical course of the disease (as measured by clinical parameters including EDSS score and the number of Gd-enhancing lesions), but 94% of patients immunized with NeuroVax developed a T-cell response. It should be noted, however, that this trial was conducted over 24 weeks, which was too short to effectively assess the clinical end points.

One caveat to the T-cell receptor vaccine approach is that preclinical data in animal models of MS are unlikely to predict the efficacy of the drug in the MS population. Animal models of MS are induced with a predefined antigen in an inbred animal with a well-defined genetic background and T-cell population; the T-cell repertoire of the human population is much more diverse, as are the etiologies of the disease. Therefore, the results seen in a well-controlled model may not be replicated in the MS patient population. Although NeuroVax may benefit some patients, the drug will likely not have a therapeutic effect in others. In addition, it is unclear how long the effects of the vaccine will last. Experts interviewed are concerned that the broad mechanism of action of this vaccine will not be efficacious and are skeptical about its potential.

The company is currently testing NeuroVax as a monotherapy and does not appear to be investigating it in combination with approved MS drugs. However, the drug's efficacy may rely primarily on the genetic background and/or etiology of the disease in some MS patients. Because the immunogenicity results are promising, we will continue to follow the development of NeuroVax with great interest; however, we do not expect the drug to be launched during our forecast period, and we do not venture a peak-year sales estimate at this time.

Tovaxin

Tovaxin is a T-cell vaccine originally developed by Opexa Pharmaceuticals for the treatment of MS. In 2004, PharmaFrontiers acquired Opexa

Pharmaceuticals and in 2005 renamed the company Opexa Therapeutics. In October 2005, Opexa announced positive interim results from two Phase I/II clinical trials. In conjunction with a development partner, INC Research, Opexa initiated a Phase IIb trial of Tovaxin in August 2006 to evaluate the safety, tolerability, and efficacy of the drug in early RR-MS patients and by January 2007 had enrolled half of the slated 150 patients. Results from this study are expected in the first half of 2008.

Tovaxin is a vaccine containing attenuated reactive T cells that are specific to three myelin proteins: myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP). These myelin protein-specific reactive T cells are derived from the patient's peripheral blood and expanded ex vivo before being reintroduced to patients in attenuated form. Patients are immunized with irradiated myelin protein-reactive T cells in an effort to deplete their own pathogenic T cells (T-cell vaccination).

The Phase IIb/III Tovaxin for Early Relapsing Multiple Sclerosis (TERMS) trial currently under way is examining the safety and efficacy of Tovaxin in RR-MS patients and patients with clinically isolated syndrome (CIS). The randomized, double-blind, placebo-controlled study is slated to enroll 150 patients, of whom 100 patients will receive five subcutaneous injections of Tovaxin at 0, 4, 8, 12, and 24 weeks and 50 patients will receive placebo; the study is expected to last for one year. The primary end point is the cumulative number of Gd-enhancing lesions as assessed by MRI at 28, 36, 44, and 52 weeks. Secondary end points include the number of new Gd-enhancing lesions following treatment completion, lesion volume, and relapse rate. The study will also examine immunological end points including the identification of biomarkers of the drug's efficacy and the effect on epitope spreading (where an immune response develops to epitopes other than the disease-causing one, specifically, in the case of autoinmune diseases, other endogenous epitopes). Enrollment is expected to be complete by mid 2007, and results are expected in 2008. A one-year open-label extension period is planned; Opexa expects to submit a separate protocol to the FDA for this phase of the trial.

A Phase I/II study had previously demonstrated the efficacy and safety of Tovaxin in ten MS patients who were intolerant of, or refractory to, currently available therapies. Patients received one of two doses of Tovaxin (6-9 million cells or 30-45 million cells) subcutaneously at 0, 4, 12, and 20 weeks. The occurrence of myelin-specific reactive T cells was measured at weeks 5, 13, 21, 28, and 52; other end points included disability progression (as measured by EDSS and the Multiple Sclerosis 29-point Impact Scale [MSIS-29], a rating scale based on both physical and psychological measurements), relapse rate, and safety.

In September 2005, Opexa presented positive results from this Phase I/II trial at the ECTRIMS meeting held in Thessaloniki, Greece. The level of reduction of myelin protein-specific reactive T cells was dose-dependent: patients who received a higher dose of Tovaxin (30-45 million cells) had a 100% reduction in the number of myelin protein-specific reactive T cells at the five-week follow-up assessment, whereas patients who received a lower dose of Tovaxin (6-9 million cells) showed less of a reduction in these T

cells. This dose-dependent effect was evident at all follow-up visits. Tovaxin reduced the annual relapse rate by 92% (relapse rate of 1.28 before Tovaxin treatment compared with 0.10 following treatment). Tovaxin also correlated with a delay in disease progression; although there was a nonstatistically significant trend (p=0.056) toward improvement in EDSS score, the reduction in myelin protein-specific reactive T cells following Tovaxin treatment strongly correlated with MSIS-29 score, suggesting that by successfully dampening a specific aspect of the immune response, Tovaxin can improve disability. Tovaxin was well tolerated by patients; injection-site pain was the most commonly reported side effect. Additional side effects included muscle weakness, abnormal vision, nasopharyngitis, and paresthesia, although none of these side effects were severe.

The positive efficacy and safety results from Phase I/II trials hold promise for the future of Tovaxin. The dramatic reduction in myelin protein-specific reactive T cells following Tovaxin treatment demonstrates the drug's potential for reducing the immune response, potentially leading to a reduction in myelin degradation and thus disease progression. However, clinical trial results have not significantly demonstrated Tovaxin's ability to delay clinical progression, presumably because of the small number of patients in the trial; it is critical for Tovaxin to demonstrate efficacy in slowing disease progression as measured by EDSS. Although a correlation between reactive T-cell levels and MSIS-29 score was reported, the MSIS-29 is not a commonly used measurement of treatment efficacy and thus cannot be the sole assessment for disability progression.

Tovaxin's formulation may be both favorable and detrimental to its success. Because it targets reactive T cells that are specific to myelin proteins known to be detected in MS patients (MBP, MOG, PLP)(Kerlero de RN, 1993; Reindl M, 1999; Steinman L, 1995), the drug will likely be effective at dampening the immune response that normally occurs in response to these T cells. However, myelin is also composed of additional proteins, some of which (i.e., myelin-associated glycoprotein [MAG]) have been shown to induce immune responses in MS patients (Soderstrom M, 1994; Steinman L, 1995; Zhang Y, 1993). Thus, Tovaxin may not entirely eliminate the immune response and may not do so in all MS patients. As a result, Tovaxin treatment will not prevent all myelin degradation.

Experts interviewed are not familiar with Tovaxin, but they are skeptical of vaccines as effective therapies for MS. The drug's inability to affect disease progression does not bode well for the drug, although its efficacy in reducing reactive T-cell numbers is promising. Moreover, it is unclear if this drug will work in all MS patients. We do not expect Tovaxin to launch for MS during our forecast period, but we continue to watch its development with interest.

Peptide-Encoding DNA Plasmids

Overview

Only one DNA-plasmid-based compound is in development for MS: Bayhill Therapeutics' BHT-3009. BHT-3009 is in Phase II trials; additional larger-scale trials are needed to fully assess its market potential. The company is

also using this plasmid technology to develop potential compounds for type 1 diabetes treatment.

Mechanism of Action

Plasmids are sequences of DNA that are distinct from chromosomal DNA; they can be manipulated to contain specific genes, which can be induced autonomously to express the desired protein. Bayhill Therapeutics has designed plasmids that express disease-specific autoantigens, i.e., MBP. These plasmids serve as a vector for delivery of MBP to MS patients: the MBP-expressing plasmids are introduced to the patients via a vaccine. Cells that take up the MBP-expressing plasmid will produce the MBP protein, which will bind TCRs and induce MBP-specific T cells to undergo anergy, thus dampening the immune response mediated by MBP-specific T cells.

BHT-3009

Bayhill Therapeutics is developing BHT-3009, a DNA vaccine against MBP, an MS-specific autoantigen. The company began Phase II trials in April 2006. BHT-3009 is also being investigated in a Phase I clinical trial in combination with the cholesterol-lowering drug atorvastatin.

BHT-3009 is designed to express the full-length form of human MBP. The compound will downregulate MBP-specific T cells, which have been detected in the CSF of MS patients following a relapse (Raine CS, 1999), thus reducing the inflammatory response (and myelin breakdown) typically induced by these T cells. Because the vaccine is specific for MBP, it will not produce a broad immunosuppressive effect, thus reducing the risk of opportunistic infections. Bayhill reports that this compound induces a low level of MBP expression over two to four weeks, which reduces the frequency of BHT-3009 administration.

A Phase II trial that was initiated in April 2006 is investigating the efficacy of BHT-3009 in RR-MS patients. The double-blind, placebo-controlled trial is slated to enroll 252 patients in the United States, Europe, and Russia. Patients will receive one of two doses of BHT-3009 (0.5 or 1.0 mg) every two weeks for six weeks, then a single dose every four weeks for an additional 38 weeks, totaling 13 doses over 44 weeks. Inclusion criteria included a diagnosis of RR-MS and an EDSS score of 0-3.5. The primary end point is the number of new Gd-enhancing lesions after one year. Secondary end points include relapse rate, disability progression (as measured by EDSS), other unspecified MRI parameters, and safety. The study is expected to be complete in the second half of 2007.

According to data presented at the 2005 ECTRIMS meeting, a Phase I/II study involving 30 relapsing MS (RR-MS and SP-MS) patients showed that vaccinated patients had reduced MBP-specific T-cell reactivity, indicating that the vaccine can alter T-cell reactivity in MS patients (Vollmer T, 2005). The randomized, double-blind, placebo-controlled study also demonstrated that no immune response to MBP was mounted following BHT-3009 treatment, suggesting that MBP-specific T cells were undergoing anergy. Similar data were presented in April 2006 at the annual meeting of the American Academy of Neurology in San Diego, as well as in May 2006

at the 16th Meeting of the European Neurological Society in Lausanne, Switzerland.

Additional preliminary data presented at the ECTRIMS meeting demonstrated that the BHT-3009 and atorvastatin combination treatment lowered the T-cell response in relapsing MS patients. Atorvastatin, like other statins, has mild immunomodulatory effects, namely shifting the cytokine profile from proinflammatory (T_H1) to anti-inflammatory (T_H2). In addition, preclinical studies suggested that atorvastatin may potentiate the effects of BHT-3009; therefore, the drugs are being investigated for safety and efficacy as a combination therapy. Patients with RR-MS or SP-MS were randomized to receive one of three doses of BHT-3009 (0.5 mg, 1.5 mg, or 3.0 mg, delivered intramuscularly) at weeks 1, 3, 5, and 9, in addition to atorvastatin (80 mg, orally) taken daily for 13 weeks. The study is ongoing, but preliminary data for two doses (0.5 mg and 1.5 mg) have been presented in abstract form. Immunologic assays demonstrated that MBP-specific T-cell proliferation was reduced in three of four BHT-3009-treated patients, although the level of reduction varied among patients (25.9% at baseline to 1.2% following treatment in the first patient; 13.3-5.4% in the second; 2.27-0.79% in the third; no change in the fourth). In addition, BHT-3009 appeared to be well tolerated; the number of adverse effects reported was not different from placebo controls, and none of the adverse effects were severe.

Most experts interviewed are not familiar with BHT-3009, and although neurologists interviewed are intrigued about the therapeutic potential of this type of drug, most are skeptical about the ability of these drugs to proceed through clinical trials. As one U.S. physician states, "I know that there are certain types of vaccines that are being developed such as myelin basic protein vaccine, and if this can be combined with a certain HLA allele in the vaccine, then it might be useful. I think it's way too far off to think of that as something that is going to be useful in the near future. I think it's possible that it might be applicable, but it's nothing that's going to come to a Phase III clinical trial in the next five years. If it does come to clinical trial, it will be much later than that."

Should BHT-3009 show clinical effectiveness in larger trials, it could become an important therapeutic option for RR-MS patients and SP-MS patients who relapse. The specificity of its immune modulation gives this vaccine the potential to be much safer than other immunomodulatory or immunosuppressive approaches. Although BHT-3009's method of administration (IM injection) is similar to that of Avonex, the potential for a less-frequent injection schedule will be more convenient for patients. In the absence of clinical data on the efficacy of BHT-3009, we cannot estimate peak-year sales for this drug, although we continue to watch its development with interest.

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Chapter 8

Emerging Neuroprotective and Remyelinating Therapies

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.5401.2615 ♦ Fax +81.3.5401.2617

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8. Emerging Neuroprotective and Remyelinating Therapies

Key Findings

- Advances in the understanding of MS pathophysiology emphasize that the lack of neuroprotective and remyelinating compounds is detrimental to successful MS treatment. However, few therapies in development target neuroprotection.
- All MS patients could potentially be treated with neuroprotective agents, which could be prescribed early in the disease process and probably in combination with immunomodulatory drugs. PP-MS patients will benefit the most from these drugs because they currently have no disease-modifying treatment options.
- One of the few neuroprotective agents in development is Acorda Therapeutics' recombinant human glial growth factor-2, which may promote remyelination. Experts warn that problems of drug delivery could hamper its development.
- Eisai is targeting cell survival with its AMPA receptor antagonist E-2007. Although clinical data are lacking, this drug has potential to counteract neuron and oligodendrocyte cell death.

"I think neuroprotection is really one of the main goals of MS research."

—Neurologist, United States

Expert Commentary: Emerging Neuroprotective Therapies in Multiple Sclerosis, 2007

Drug	Expert Opinion
Recombinant human glial growth factor-2 (Acorda Therapeutics)	"I think it's a good strategy. The growth factors have had a terrible, terrible run. The problem is having a delivery system that gets the growth factors to the right place. I think if people can develop a delivery system, then a number of these growth factors are going to be very effective. The question is developing the delivery system, and no one has come up with an innovative strategy yet." — Neurologist, United States "I'm a little concerned about growth factors because if they are given systemically, they will increase growth in different organ systems and perhaps they will induce tumors or any kind of growth of organs. I'm skeptical about growth factors." — Neurologist, Germany
E-2007 (Eisai)	"Regarding newer drugs, we are quite interested in E-2007, the Eisai drug, which is an AMPA receptor antagonist. I think it would be an interesting one." — Neurologist, United Kingdom "I understand the mechanism of action, but I think there are some preclinical controversial data about the role of AMPA receptors. Nevertheless, it is really an interesting way, but I do not have any knowledge clinically." — Neurologist, France

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Early-Stage Pipeline Status of Neuroprotective Drugs by Class for Multiple Sclerosis, 2007

Key Classes	PC	I	II
Peptide growth factors	●	●	
AMPA receptor antagonists	●		●
Remyelinating agents	●		
Other neuroprotective agents	●●		●●

● = one drug.

Note: Numbers reported here are Decision Resources estimates of key agents based on review of multiple publicly available databases and information.

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Overview

Neuroprotection and neuronal survival are critical unmet needs in multiple sclerosis (MS) therapy; the paucity of compounds in clinical development for neuroprotection and oligodendrocyte survival/remyelination demonstrates the significant opportunity for such therapies in MS. One of the most promising therapies in this category, recombinant human glial growth factor-2 (rhGGF2, Acorda Therapeutics), promotes the proliferation of oligodendrocytes, the myelin-producing cells of the CNS. A second therapy, Eisai's E-2007, may promote survival of both oligodendrocytes and neurons. These therapies should be efficacious in all MS patients because demyelination and degeneration are hallmarks of both relapsing (RR-MS) and chronic forms of MS (CP-MS, including secondary-progressive [SP-MS] and primary-progressive [PP-MS]). If these therapies could be administered early enough in the disease process, they could significantly delay disease onset and halt or delay the development of disability, even potentially reversing it. However, both therapies are in early stages of development, and their development is hampered because there are no methods to accurately assess neuroprotection. In addition, Acorda must resolve delivery problems before rhGGF2 can proceed to clinical development.

Several other companies, including Teva, Sanofi-Aventis, and Gemac Bio, are researching compounds with neuroprotective qualities. Teva is investigating novel compounds for MS, including TV-3606, which is in preclinical stages. Although its mechanism of action is not clear, this compound, according to Teva, may have both anti-inflammatory and neuroprotective functions.

Sanofi-Aventis was developing xaliproden, a nerve growth factor (NGF) agonist and a serotonin (5-HT) receptor agonist, as an oral therapy for MS. However, by September 2006, it appeared that the company had reprioritized the drug for the treatment of Alzheimer's disease (AD); two Phase III trials are ongoing for this indication. Xaliproden has been shown in vitro and in animal studies to have properties similar to those of NGF and brain-derived neurotrophic factor (BDNF), two related neurotrophic factors; neurotrophic factors are vital to maintaining neuronal health and survival.

Indeed, in animal models, xaliproden appears to induce the expression of NGF and BDNF, induce neuronal growth, and function as a neuroprotectant by reducing neuron death. MS experts interviewed are very interested in xaliproden because of its novel mechanism of action. Its neuroprotective qualities would prove beneficial for all MS subtypes, including progressive forms of MS for which few therapeutic options are available. If xaliproden is approved for AD, it may be prescribed off-label for MS patients.

Gemac Bio is developing GEM-SP specifically for SP-MS patients, though little information on the drug's development is available. Gemac Bio announced in a February 2006 press release that a small Phase IIa trial in which 22 SP-MS patients were treated with GEM-SP orally for 6-18 months showed that the drug was safe and well tolerated by all patients; Phase IIb trials are planned for the first half of 2007. The drug's mechanism of action is not clear, although the company states that the drug is a combination of small molecules linked to a peptide carrier and that the drug has both neuroprotective and immunomodifying properties. Gemac Bio is also conducting preclinical studies of a second compound, GEM-RR, for the treatment of RR-MS. Therapeutic options for SP-MS patients are available only for those SP-MS patients who are relapsing, so a neuroprotective therapy would provide a much needed option for all SP-MS patients.

The protein erythropoietin is also being investigated as a potential neuroprotective agent for MS; the Max-Planck Institute for Experimental Medicine completed a Phase II clinical trial in September 2006. Although little information about the trial is available, the open-label trial examined the efficacy of two unspecified doses of erythropoietin on walking distance and Expanded Disability Status Scale (EDSS) after 24 weeks of treatment. The compound is also in development for stroke and schizophrenia. Stem Cell Therapeutics announced in a September 2006 press release that it has acquired the option to obtain an MS clinical program from the Max-Planck Institute. Erythropoietin, which binds to receptors on immature red blood cells and promotes the cells to mature, represents an alternative mechanism that may alter the inflammatory cytokine profile, thus dampening the immune response seen in MS. In addition, erythropoietin has demonstrated some efficacy in preventing cell death in stroke and in schizophrenic patients, suggesting that the compound is also neuroprotective. However, whether erythropoietin will prove adequate at dampening the MS immune response or promoting neuronal and oligodendrocyte survival is unclear.

In addition, Biogen Idec is investigating the myelination-inhibitory protein Lingo-1 as a potential therapeutic target in MS. Lingo-1, which is expressed by oligodendrocytes and neurons, prevents oligodendrocytes from producing myelin (Lee X, 2007; Mi S, 2005). Although the program is in preclinical stages, researchers at Biogen Idec report that inhibition of Lingo-1 permits axon remyclination, suggesting that blocking Lingo-1 may promote remyelination in MS patients. However, it is likely that inhibition of multiple factors, including Lingo-1, is required for complete remyelination to occur in MS patients.

Table 8-1 summarizes the key neuroprotective drug therapies in development for MS.

Table 8-1

Emerging Neuroprotective Therapies in Development for Multiple Sclerosis, 2007

Compound	Status	Marketing Company	Peak-Year Sales Potential[a] ($MM)
Glial growth factors			
Recombinant human GGF2			Lack of data precludes estimate
United States	PC	Acorda Therapeutics	
Europe	—	—	
Japan	—	—	
AMPA receptor antagonists			
E-2007			Lack of data precludes estimate
United States	II	Eisai	
Europe	II	Eisai	
Japan	I	Eisai	

a. Represents peak-year sales in the major pharmaceutical markets for the indication under study only. Methodology is explained in the "Emerging Neuroprotective and Remyelinating Therapies" chapter of the text.

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GGF2 = glial growth factor 2; PC = Preclinical (including discovery).

Note: Status is based on databases such as R&D Insight and the Investigational Drugs Database (IDdb); periodicals such as *Scrip*, the FDC's *Pink Sheet*, and *Marketletter*; company reports and press releases; and industry contacts.

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Emerging Therapies Positioning

Because all current MS therapies function only as immunomodulators, significant opportunity exists in the MS market for neuroprotective/remyelinating agents. The neuroprotective/remyelinating compounds are all in early stages of development, so it is difficult to say with certainty how efficacious these drugs will be and whether they will come to market. The majority of experts express intense interest in neuroprotective compounds because, as one U.S. neurologist states, "[they] would be applicable to the early patients but also to patients with progressive MS because that's the patient who might not respond to suppression of inflammation but might very well respond to a neuroprotective drug." Given the high unmet need for neuroprotective drugs in MS and physicians' receptiveness to these new therapies, we expect that if a compound shows even modest efficacy in promoting remyelination and/or neuroprotection, it will receive fast-track status from the FDA.

An ideal neuroprotective/remyelinating agent would not only be efficacious but also have a very favorable safety profile so that it could be administered to early-stage MS patients. Indeed, recent evidence suggests that demyelination and neuronal damage occur very early in the course of the disease (Kuhlmann T, 2002; Rovaris M, 2005). However, we expect that even neuroprotective drugs with slightly less-favorable safety profiles will launch for MS because of the high unmet need for these agents.

When neuroprotective drugs are launched, they will enjoy significant uptake by all MS populations. These compounds will likely become first-line therapies for patients with aggressive RR-MS and those with chronic forms of the disease (SP-MS and PP-MS), for which few therapeutic options currently exist. Although these drugs may be used as monotherapy, for patients with RR-MS, these compounds will likely be used in conjunction with immunomodulatory drugs. As one neurologist explains, "What I think is likely to happen is that we would be using more of a combinatorial regimen, combining drugs that perhaps reduce the inflammatory response with drugs that may promote neural regeneration or perhaps some repair mechanism within the brain." According to another expert, "When you think of combination therapy, you can combine different immunomodulatory drugs, but the good thing would be to put one immunomodulatory drug with a remyelination agent, with a neuroprotective agent. That would be a very synergistic combination." Experts note that because neuroprotective agents and immunomodulatory drugs act on two separate aspects of MS, these drugs will likely be able to be used in combination without increasing the incidence of severe side effects (as seen with the combination of two immunomodulatory agents).

Although the vast majority of experts state that the development of neuroprotective drugs is needed for MS treatment, some doubt they will be successfully developed. According to one expert, "It would be a very, very interesting option to develop neuroprotective drugs, but it is very, very difficult to do because we don't know the etiology of the disease--it's practically impossible to find neuroprotectants. What are we protecting? We don't know exactly." In addition, evaluating the efficacy of these agents may prove challenging. Nevertheless, most experts interviewed are optimistic that these hurdles will be overcome. One neurologist states, "This [neuroprotection] is a very important issue that should be solved because neuroprotection and regeneration are very important for patients in the more advanced stages of disease and in the chronic-progressive patients."

Glial Growth Factors

Overview

The only recombinant human glial growth factor in development is Acorda Therapeutics' rhGGF2. Although it is only in preclinical development, experts interviewed are very interested in this compound because it may be the first drug therapy that can repair myelin damage caused by MS.

Mechanism of Action

RhGGF2 is a neuroregulatory signaling and growth factor that is associated with the proliferation and survival of oligodendrocytes, the myelinating cells of the central nervous system (CNS) (Cannella B, 1998; Canoll PD, 1996; Marchionni MA, 1999; Milner R, 1997). By preserving oligodendrocytes, this agent may protect the myelin sheath from the damage that occurs in MS as a result of the release of toxic factors such as glutamate and free radicals generated by the proinflammatory immune response.

Recombinant Human Glial Growth Factor-2

Originally, Cambridge Neuroscience, which was acquired by CeNeS Pharmaceuticals, was developing rhGGF2. An agreement in 1998 gave exclusive worldwide manufacturing and marketing rights to Bayer; however, this collaboration was terminated in April 2002. CeNeS was developing the compound in preclinical studies until it closed its U.S. facilities in August 2002 and reorganized its pipeline to focus on agents for pain. In November 2002, Acorda Therapeutics acquired an exclusive worldwide lieense from CeNeS for rhGGF2. Acorda is conducting preclinical studies of rhGGF2 for the treatment of MS.

RhGGF2's preservation of oligodendrocytes holds promise for its role in MS therapy; indeed, rhGGF2 has been shown in animal studies to promote remyelination (Cannella B, 1998). In addition, rhGGF2 appears to dampen free-radical release from activated microglial cells in vitro (Dimayuga FO, 2003).

In preclinical studies, positive effects were seen in both the acute and chronic phases of experimental autoimmune encephalomyelitis (EAE), a rodent model of MS (Cannella B, 1998; Marchionni MA, 1999). When administered during the acute phase (before appearance of clinical signs), rhGGF2 (dosed subcutaneously daily for ten days) demonstrated a dose-dependent delay in clinical onset; symptoms peaked 17-20 days after the induction of EAE in rhGGF2-treated animals and 10-11 days after induction in placebo-treated animals. In addition, rhGGF2-treated animals (doses of 0.2 mg/kg, 0.6 mg/kg, and 2.0 mg/kg) displayed a dose-dependent reduction in the severity of clinical symptoms versus controls; the mean clinical score for all treated groups combined was 50% lower than the score of control animals. Furthermore, chronically treated animals displayed markedly reduced lesion activity. Animals treated with rhGGF2 (dosed subcutaneously three times weekly with 0.02 mg/kg or 0.2 mg/kg rhGGF2) during the chronic phases of EAE demonstrated a significant reduction in clinical score throughout the treatment period. The mean clinical scores for rhGGF2-treated animals were 2.17 and 2.11 for 0.02 mg/kg and 0.2 mg/kg, respectively; the mean clinical score for controls was 2.51 ($p<0.01$). This benefit continued for nearly 40 days after treatment ceased ($p<0.01$). Furthermore, treated animals experienced significantly fewer relapses than controls, and this reduction in relapse rate was maintained for up to 36 days after cessation of treatment; however, the effect was not dose-dependent, which raises questions as to the therapeutic effect of rhGGF2.

Most importantly, treated animals demonstrated diminished autoimmune demyelination and significantly enhanced CNS remyelination when compared with controls (1.05 for treated animals [all doses pooled] and 0.5 for controls [$p<0.007$]). Markers of remyelination were induced in rhGGF2-treated animals but not in controls, suggesting that rhGGF2 was effective in inducing remyelination in the treated animals. Finally, rhGGF2 treatment appeared to increase expression of the anti-inflammatory cytokines IL-4 and IL-10. To what extent these findings in controlled animal models will show potential for MS patients remains to be shown. In particular, it is unclear at this juncture whether chronic treatment with rhGGF2 could cause Schwann

cells (the glial cells of the peripheral nervous system [PNS] that form PNS myelin) to overgrow (hyperplasia) and even form Schwannomas or Schwann cell tumors in treated patients.

Delivery of the drug remains a problem as well. As one U.S. neurologist explains, "I don't know how you would be administering the drug. I mean, is this a drug that is going to have to be given intraventricularly into some kind of reservoir in the spinal fluid? It's not likely to be taken up by an injection and get into the brain. I think getting to the CNS might be an issue." Because the drug cannot be delivered peripherally without causing unacceptable side effects such as pain, the drug would theoretically have to be delivered directly to the CSF via a spinal injection (intrathecally), which is an unacceptable solution. Acorda must overcome this shortcoming before the drug can be commercially viable.

Experts interviewed remain exeited about rhGGF2 because it could be the first therapy that can reverse or prevent some of the damage done to myelin in MS. However, experts note, Acorda will have difficulty designing trials that measure neuroprotection because researchers still do not agree on the best way to demonstrate this result. Most experts anticipate that this type of drug will be used primarily in combination with disease-modifying drugs to provide enhanced efficacy over monotherapy; some experts also expect this type of drug to be used as monotherapy, particularly in chronic-progressive patients. Trials demonstrating neuroprotective efficacy of the drug in combination with currently available disease-modifying drugs may prove particularly challenging if the drug shows only modest efficacy. However, given that the drug has not reached human trials, the majority of neurologists interviewed do not expect rhGGF2 to be launched within the next 15 years. Given the developmental hurdles that Acorda must overcome and without knowing the potential level of therapeutic effect or the safety profile this treatment may have in humans, we do not include rhGGF2 in our forecast and are unable to forecast peak-year sales at this time, although we continue to watch this drug with interest.

AMPA Receptor Antagonists

Overview

Only one company, Eisai, is investigating the use of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists for the treatment of MS, and development is in early stages. Eisai's E-2007 entered Phase II trials for MS in Europe in March 2003 and in the United States in November 2003. The drug is in Phase I studies for this indication in Japan. Teva's AMPA receptor antagonist talampanel was originally developed by Ivax; in January 2006, Teva acquired Ivax and it appears that development of talampanel has been reprioritized for glioma and epilepsy. Therefore, we focus our discussion on E-2007. Eisai is also developing E-2007 for Parkinson's disease and anticipates filing regulatory submissions for this indication in the United States and Europe in 2007.

Mechanism of Action

AMPA receptors, which bind the excitatory neurotransmitter glutamate, are present on both neurons and oligodendrocytes. During inflammation in both EAE and MS, lymphocytes, brain microglia, and macrophages release excessive amounts of glutamate, which can then activate AMPA receptors (Steinman L, 2000). Overstimulation of AMPA receptors can precipitate excitotoxic cell death, not only for neurons but also for oligodendrocytes, by allowing excessive amounts of sodium and calcium in a subclass of AMPA receptors to enter the cells (McDonald JW, 1998). High sodium concentrations induce a massive influx of water into neurons along a concentration gradient and an influx of negatively charged chloride (Cl-) ions along an electrostatic gradient. The combination of pronounced cellular edema (swelling), low pH, and adenosine triphosphate (ATP) depletion in neurons and in oligodendrocytes causes several morphological changes that result in reduced protein synthesis, inappropriate activation of calcium-activated proteases, and free-radical release, thereby causing cell death of neurons and oligodendrocytes by excitotoxicity. Blockade of AMPA receptors has been found effective in suppressing damage in EAE (Steinman L, 1999). The blockade of AMPA receptors does not appear to influence the immune response to myelin antigens, but it protects oligodendrocytes from immune-mediated damage by an unknown mechanism.

E-2007

In its MARS (Multiple Sclerosis AMPA Receptor Selective) program, Eisai is investigating the potential of AMPA receptor antagonists in MS. Its lead candidate is E-2007. The compound is in Phase II trials in Europe and the United States and in Phase I trials in Japan as of May 2005; plans for regulatory submissions for MS in the United States and Europe have not been announced. E-2007 is also in development for Parkinson's disease and epilepsy. No new information on the development of E-2007 is available at the time of this writing.

Glutamate excitotoxicity mediated by the AMPA receptor damages not only neurons but also the myelin-producing oligodendrocytes (McDonald JW, 1998). By antagonizing the AMPA receptor, E-2007 may provide neuroprotection to MS patients by protecting both neurons and oligodendrocytes from cell death (Matute C, 2001).

Although no clinical data have been released, preclinical data support the theory that E-2007 has neuroprotective qualities, albeit these results are in rodent models of MS. Oral doses of E-2007 (30 mg/kg) significantly reduced leukocyte infiltration, demyelination, and axonal damage in the mouse model of EAE (Yamauchi T, 2002). E-2007 also significantly ameliorated disease severity throughout the experiment (nine weeks). In a rat model of EAE, oral E-2007 reversed axonal damage associated with EAE (Smith T, 2002b). In addition, the drug dose-dependently improved neurological status without affecting CNS inflammation or peripheral myelin basic protein (MBP) antibody production. Reduced axonal/neuronal damage correlated with the reduction in disease severity.

Eisai suggests that its potential neuroprotectant therapy E-2007 may complement current disease-modifying treatments such as immunosuppressants and immunomodulatory therapies. Despite physician wariness about the potential for severe side effects associated with combining multiple immunomodulatory agents, most experts interviewed anticipate using neuroprotective agents in combination with immunomodulatory drugs; they say that the risk of severe side effects is no greater because the agents have differing mechanisms of action. In the rat EAE model, oral E-2007 administered in combination with an IFN-β therapy improved neurological status more effectively than either therapy given alone (Smith T, 2002a).

Although the E-2007 data released are limited, the drug's potential to delay or prevent axonal damage is exciting to experts interviewed. Researchers surmise that axonal damage is the pathological correlate of irreversible neurological impairment in MS (Trapp BD, 1998). Currently available disease-modifying drugs—IFN-β therapies, glatiramer acetate (Teva's Copaxone), and natalizumab (Biogen Idec/Elan's Tysabri)—can reduce the number of exacerbations and delay lesion development, but none of these drugs appears to address axonal damage.

Most experts interviewed are not familiar with E-2007; those who are aware of it are withholding judgment until clinical trial data are available. Experts interviewed are not convinced that the blockade of AMPA receptors alone will prevent all axonal damage, given the multiple cytotoxic factors known to be present in EAE lesions. They anticipate that such a neuroprotective drug could be administered early in the disease process, when oligodendrocytes are damaged, and the drug would be administered on a chronic basis for several years—both attractive commercial qualities. Most experts, while hopeful such a therapy will come to market, are skeptical about its chances of success. AMPA receptor antagonists have been tested in other indications—such as stroke—for neuroprotection, but no agent has been able to reach Phase III trials, owing to unacceptable adverse events. Other hindrances for neuroprotective drugs in stroke include the failure of encouraging animal trial results to translate into good human trial data and the inability of clinical trials to gauge neuroprotection results as clinical symptom improvements. E-2007 would theoretically prevent excitotoxicity in both neurons and oligodendrocytes—it is possible that the drug will display more efficacy than other neuroprotective agents because the drug protects two cell types. Many experts note that designing trials that can demonstrate neuroprotection will be a large obstacle for Eisai; determining the best way to measure axonal injury and neuronal death is still a budding science in MS, and appropriate measures are still being debated.

We do not expect E-2007 to come to market before the end of our forecast period because of the difficulty in designing trials to demonstrate E-2007's neuroprotective qualities, and we do not provide a peak-year sales estimate at this time. Furthermore, without clinical data and based on physicians' skepticism of the therapy's potential for success, we are unable to forecast with confidence that the drug will make it to market after this point. However, if this drug can prevent axonal damage in humans and provide measurable clinical benefit to patients, it could achieve blockbuster status. Because it would be the first neuroprotective agent to market in MS, because

it is an oral agent, and because it could be delivered to all MS subpopulations as soon as the disease is diagnosed and on a chronic basis (if the side-effect profile proves favorable), the drug would experience significant market uptake. We continue to watch its development closely.

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Pharmacor

MULTIPLE SCLEROSIS 2005-2020

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Chapter 9

Market Outlook

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.5401.2615 ♦ Fax +81.3.5401.2617

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9. Market Outlook

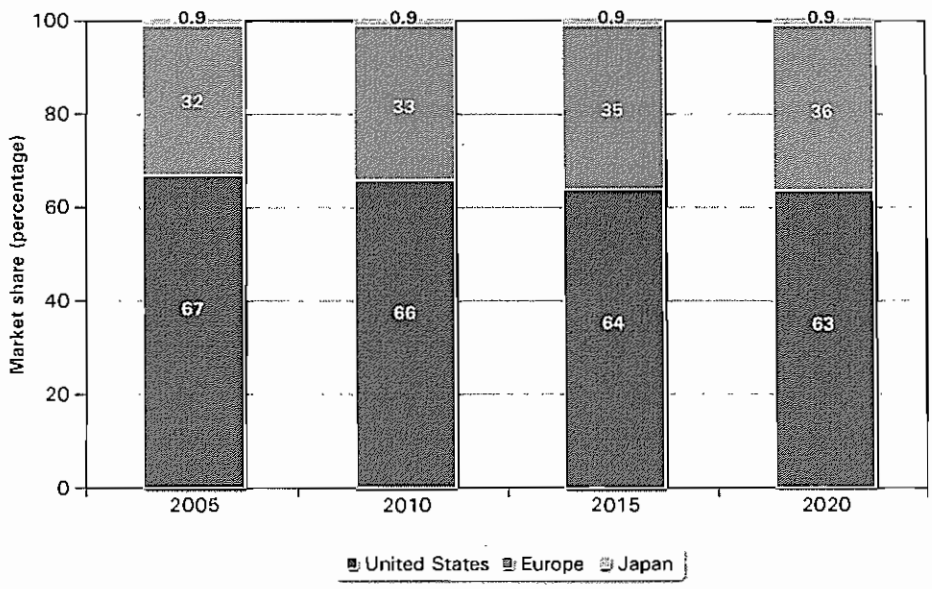
Key Findings

- The MS market will grow by nearly 40% from $4.0 billion in 2005 to more than $5.5 billion in 2020, driven by the emergence of new therapies and increases in the diagnosed and drug-treated patient populations.
- Novel immunomodulators and immunosuppressants will capture 32% of major-market sales in 2020. These agents will provide patients with additional therapeutic options, although most demonstrate only modest efficacy improvements over current therapies.
- Of the emerging agents, Novartis/Mitsubishi's FTY-720 will achieve the greatest market success, capturing $870 million in major-market sales and 16% of market share in 2020. BioMS Medical's MBP-8298, which is in development primarily for the SP-MS population, will achieve modest success in its niche patient population, earning approximately $275 million in 2020.
- Biogen Idec's Avonex and glatiramer acetate (Teva's Copaxone) will dominate the market through 2010 but will be outperformed by Merck Serono/Pfizer's Rebif from 2010 to 2020. Follow-on products to IFN-β-1b (Bayer Schering Pharma's Betaferon/Berlex's Betaseron), Rebif, and glatiramer acetate will moderately boost sales beginning in 2007 but will only temper the decline induced by biogeneric competition beginning in 2012.

"I don't know how much money there still is in the beta interferon business because I think they have already reached a ceiling effect. In the future, once other drugs become available, the importance of the interferons will probably be reduced."

—Neurologist, Germany

Multiple Sclerosis Market Share by Region, 2005-2020



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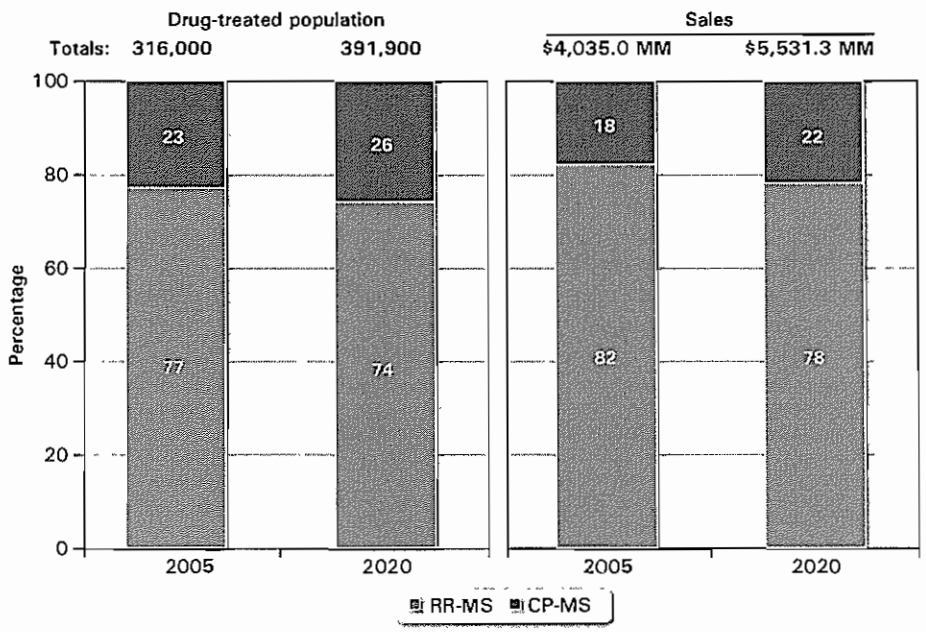
Drug-Treatment Rates and Sales by Disease Category, 2005 and 2020



CP-MS = Chronic-progressive multiple sclerosis; RR-MS = Relapsing-remitting multiple sclerosis.

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Overview

We estimate that sales of disease-modifying drugs for multiple sclerosis (MS) in the seven major pharmaceutical markets that we cover (United States, France, Germany, Italy, Spain, United Kingdom, and Japan) will grow modestly over our study period, from $4 billion in 2005 to $5.5 billion in 2020 (Table 9-1). This growth will be driven primarily by increases in diagnosis rates, overall drug-treatment rates, and an increased number of therapeutic options on the market. Growth will occur in all markets but particularly in the European markets. (Note that we restrict our analysis in this report to disease-modifying drugs, which affect the underlying cause of the disease; we do not consider drugs used to treat the symptoms of MS, such as fatigue or spasticity.) Growth will be driven by increased treatment of both relapsing-remitting MS (RR-MS) and chronic-progressive MS (CP-MS). Tables 9-2 and 9-3 present sales of drugs to treat RR-MS and CP-MS, respectively.

IFN-β therapies will remain the top-selling drug class in the MS market during our study period. In 2005, combined sales of IFN-β therapies totaled nearly $3 billion, representing approximately 73% of total sales (Figure 9-1; Figure 9-2). We forecast that these agents' market share will decline significantly, to approximately 45% in 2020, because of the availability of additional therapies for MS patients and, more modestly, because of the availability of biogeneric versions of the IFN-βs.

Table 9-1

Sales of Drugs to Treat Multiple Sclerosis (All Populations) in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($ MM)				Growth (%/year) 2005-2010	Growth (%/year) 2010-2015	Growth (%/year) 2015-2020
	2005	2010	2015	2020			
United States							
Recombinant interferons	1,845.3	1,904.5	1,636.3	1,437.5	0.6	(3.0)	(2.6)
Interferon β-1b	399.4	360.8	332.0	293.5	(2.0)	(1.6)	(2.4)
Interferon β-1a (Avonex)	1,024.9	976.2	668.1	495.0	(1.0)	(7.3)	(5.8)
Interferon β-1a (Rebif)	421.0	567.5	636.2	649.1	6.2	2.3	0.4
Altered peptide ligands	807.8	783.4	628.18	629.0	(0.6)	(4.3)	0.0
Glatiramer acetate	807.8	783.4	524.3	424.2	(0.6)	(7.7)	(4.1)
MBP-8298	0.0	0.0	103.8	204.7	N.M.	N.M.	14.5
Chemotherapeutics	38.6	25.2	14.3	8.8	(8.1)	(10.7)	(9.4)
Mitoxantrone	37.1	24.2	13.4	7.9	(8.2)	(11.2)	(9.9)
Cyclophosphamide	1.4	1.0	0.9	0.8	(6.6)	(1.7)	(3.0)
Methotrexate	0.1	0.0.	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	5.5	31.0	159.0	214.5	41.5	38.7	6.2
Azathioprine	3.0	1.8	1.9	2.0	(9.8)	1.4	0.8
Teriflunomide	0.0	0.0	38.6	79.9	N.M.	N.M.	15.7
Cladribine	0.0	26.6	115.7	130.8	N.M.	34.1	2.5
Mycophenolate mofetil	2.5	2.5	2.8	1.7	0.4	2.3	(9.1)
Monoclonal antibodies	21.9	254.0	375.4	482.8	63.3	8.1	5.2
Natalizumab	21.9	216.0	316.2	414.5	58.1	7.9	5.6
Daclizumab	0.0	38.0	59.2	68.3	N.M.	9.3	2.9
Corticosteroids	2.4	2.6	2.7	2.8	1.1	0.9	0.5
Methylprednisolone	2.4	2.5	2.7	2.7	1.1	0.9	0.5
Other corticosteroids	0.0	0.0	0.0.	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	59.2	561.7	715.9	N.M.	56.8	5.0
FTY-720	0.0	59.2	505.2	599.9	N.M.	53.5	3.5
BG-12	0.0	0.0	28.2	58.0	N.M.	N.M.	15.5
Laquinimod	0.0	0.0	28.2	58.0	N.M.	N.M.	15.5
Total	2,721.4	3,059.9	3,377.5	3,491.3	2.4	2.0	0.7
Europe							
Recombinant interferons	1,061.1	1,151.2	1,090.1	1,020.7	1.6	(1.1)	(1.3)
Interferon β-1b	305.8	275.4	214.2	178.2	(2.1)	(4.9)	(3.6)
Interferon β-1a (Avonex)	334.3	362.6	308.1	265.6	1.6	(3.2)	(2.8)
Interferon β-1a (Rebif)	421.0	513.2	567.8	576.9	4.0	2.0	0.3
Altered peptide ligands	199.2	229.4	254.8	235.1	2.9	2.1	(1.6)
Glatiramer acetate	199.2	229.4	215.0	166.0	2.9	(1.3)	(5.0)
MBP-8298	0.0	0.0	39.9	69.1	N.M.	N.M.	11.6
Chemotherapeutics	7.8	6.8	5.4	4.3	(2.8)	(4.4)	(4.7)
Mitoxantrone	7.4	6.4	5.1	4.1	(2.7)	(4.4)	(4.6)
Cyclophosphamide	0.4	0.3	0.3	0.2	(2.8)	(2.6)	(6.4)
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	5.0	20.0	75.4	128.4	32.1	30.4	11.2
Azathioprine	2.5	2.2	1.8	1.4	(2.6)	(4.0)	(5.5)
Teriflunomide	0.0	0.0	25.5	53.0	N.M.	N.M.	15.8

(continued)

Table 9-1 (cont.)

Sales of Drugs to Treat Multiple Sclerosis (All Populations) in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($ MM)				Growth (%/year) 2005-2010	Growth (%/year) 2010-2015	Growth (%/year) 2015-2020
	2005	2010	2015	2020			
Cladribine	0.0	15.2	46.1	72.5	N.M.	24.8	9.5
Mycophenolate mofetil	2.4	2.6	2.0	1.4	1.2	(4.7)	(6.8)
Monoclonal antibodies	0.0	104.2	193.4	249.9	N.M.	13.2	5.3
Natalizumab	0.0	104.2	158.1	208.4	N.M.	8.7	5.7
Daclizumab	0.0	0.0	35.3	41.5	N.M.	N.M.	3.3
Corticosteroids	4.1	3.9	4.1	4.0	(0.9)	1.0	(0.5)
Methylprednisolone	4.0	3.8	4.0	3.9	(0.9)	1.0	(0.5)
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	227.9	349.7	N.M.	N.M.	8.9
FTY-720	0.0	0.0	188.3	268.4	N.M.	N.M.	7.4
BG-12	0.0	0.0	19.8	40.6	N.M.	N.M.	15.5
Laquinimod	0.0	0.0	19.8	40.6	N.M.	N.M.	15.5
Total	1,277.2	1,515.4	1,851.1	1,992.0	3.5	4.1	1.5
France							
Recombinant interferons	223.0	224.9	197.1	178.7	0.2	(2.6)	(1.9)
Interferon β-1b	50.6	41.3	32.9	27.8	(3.9)	(4.5)	(3.3)
Interferon β-1a (Avonex)	107.2	105.0	76.0	57.6	(0.4)	(6.3)	(5.4)
Interferon β-1a (Rebif)	65.3	78.6	88.3	93.3	3.8	2.3	1.1
Altered peptide ligands	34.5	50.2	52.9	47.5	7.9	1.1	(2.1)
Glatiramer acetate	34.4	50.2	45.4	34.5	7.9	(2.0)	(5.4)
MBP-8298	0.0	0.0	7.5	13.0	N.M.	N.M.	11.6
Chemotherapeutics	2.0	1.8	1.5	1.2	(2.1)	(2.8)	(4.9)
Mitoxantrone	1.8	1.7	1.4	1.1	(2.0)	(2.8)	(5.0)
Cyclophosphamide	1.0	0.1	0.0	0.0	(0.7)	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	2.8	6.4	17.1	26.1	17.7	21.8	8.9
Azathioprine	0.4	0.4	0.3	0.2	(0.8)	(4.9)	(6.8)
Teriflunomide	0.0	0.0	4.6	9.4	N.M.	N.M.	15.3
Cladribine	0.0	3.4	10.2	15.1	N.M.	24.3	8.2
Mycophenolate mofetil	2.4	2.6	2.0	1.4	1.2	(4.7)	(6.9)
Monoclonal antibodies	0.0	22.1	37.5	44.8	N.M.	11.1	3.6
Natalizumab	0.0	22.1	28.7	34.8	N.M.	5.3	3.9
Daclizumab	0.0	0.0	8.8	10.0	N.M.	N.M.	2.5
Corticosteroids	0.8	0.8	0.8	0.8	(0.6)	0.6	(0.1)
Methylprednisolone	0.8	0.8	0.8	0.8	(0.6)	0.6	(0.1)
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	49.6	73.8	N.M.	N.M.	8.3
FTY-720	0.0	0.0	42.5	59.2	N.M.	N.M.	6.9
BG-12	0.0	0.0	3.6	7.3	N.M.	N.M.	15.3
Laquinimod	0.0	0.0	3.6	7.3	N.M.	N.M.	15.3
Total	263.0	306.2	356.7	373.0	3.1	3.1	0.9

(continued)

Table 9-1 (cont.)

Sales of Drugs to Treat Multiple Sclerosis (All Populations) in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($ MM)				Growth (%/year) 2005-2010	Growth (%/year) 2010-2015	Growth (%/year) 2015-2020
	2005	2010	2015	2020			
Germany							
Recombinant interferons	475.1	508.0	456.8	416.2	1.3	(2.1)	(1.8)
Interferon β-1b	154.2	137.7	104.9	85.7	(2.2)	(5.3)	(4.0)
Interferon β-1a (Avonex)	130.5	140.3	116.9	105.1	1.5	(3.6)	(2.1)
Interferon β-1a (Rebif)	190.4	230.0	235.0	225.3	3.9	0.4	(0.8)
Altered peptide ligands	118.5	108.6	115.7	102.0	(1.7)	1.3	(2.5)
Glatiramer acetate	118.5	108.6	100.3	74.8	(1.7)	(1.6)	(5.7)
MBP-8298	0.0	0.0	15.4	27.2	N.M.	N.M.	12.0
Chemotherapeutics	4.5	3.7	2.8	2.2	(3.5)	(5.5)	(5.0)
Mitoxantrone	4.2	3.6	2.7	2.1	(3.3)	(5.5)	(4.7)
Cyclophosphamide	0.2	0.1	0.1	0.0	(5.2)	(4.5)	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	1.7	8.1	31.5	51.5	36.9	31.3	10.3
Azathioprine	1.7	1.5	1.2	0.9	(2.9)	(4.2)	(6.1)
Teriflunomide	0.0	0.0	9.4	19.3	N.M.	N.M.	15.5
Cladribine	0.0	6.6	21.0	31.3	N.M.	25.9	8.4
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	42.8	71.5	85.7	N.M.	10.8	3.7
Natalizumab	0.0	42.8	57.2	69.0	N.M.	6.0	3.9
Daclizumab	0.0	0.0	14.4	16.6	N.M.	N.M.	3.0
Corticosteroids	2.1	1.6	1.6	1.5	(5.2)	0.4	(1.0)
Methylprednisolone	2.1	1.6	1.6	1.5	(5.2)	0.4	(1.0)
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	92.1	140.0	N.M.	N.M.	8.7
FTY-720	0.0	0.0	77.8	111.2	N.M.	N.M.	7.4
BG-12	0.0	0.0	7.1	14.4	N.M.	N.M.	15.1
Laquinimod	0.0	0.0	7.1	14.4	N.M.	N.M.	15.1
Total	601.9	672.9	772.0	799.0	2.3	2.8	0.7
Italy							
Recombinant interferons	179.2	190.3	184.0	172.4	1.2	(0.7)	(1.3)
Interferon β-1b	38.7	34.0	28.6	24.0	(2.5)	(3.4)	(3.5)
Interferon β-1a (Avonex)	51.8	56.5	47.1	40.0	1.8	(3.6)	(3.2)
Interferon β-1a (Rebif)	88.7	99.7	108.3	108.4	2.4	1.7	0.0
Altered peptide ligands	21.7	28.1	30.3	30.6	5.3	1.5	0.2
Glatiramer acetate	21.7	28.1	23.6	18.2	5.3	(3.4)	(5.1)
MBP-8298	0.0	0.0	6.7	12.4	N.M.	N.M.	13.1
Chemotherapeutics	0.8	0.6	0.5	0.4	(3.6)	(5.8)	(2.8)
Mitoxantrone	0.7	0.6	0.4	0.4	(3.5)	(5.9)	(2.8)
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.3	3.7	10.1	19.4	62.6	22.4	14.0
Azathioprine	0.3	0.3	0.2	0.1	(4.0)	(5.1)	(5.5)
Teriflunomide	0.0	0.0	4.5	9.1	N.M.	N.M.	15.3

(continued)

Table 9-1 (cont.)

Sales of Drugs to Treat Multiple Sclerosis (All Populations) in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($ MM)				Growth (%/year) 2005-2010	Growth (%/year) 2010-2015	Growth (%/year) 2015-2020
	2005	2010	2015	2020			
Cladribine	0.0	3.4	5.4	10.2	N.M.	9.8	13.3
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	16.7	34.2	45.9	N.M.	15.4	6.1
Natalizumab	0.0	16.7	27.6	38.4	N.M.	10.6	6.8
Daclizumab	0.0	0.0	6.5	7.5	N.M.	N.M.	2.8
Corticosteroids	0.5	0.5	0.5	0.5	1.1	0.2	0.1
Methylprednisolone	0.5	0.5	0.5	0.5	1.3	0.2	0.1
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	37.6	56.6	N.M.	N.M.	8.5
FTY-720	0.0	0.0	30.7	42.8	N.M.	N.M.	6.8
BG-12	0.0	0.0	3.5	6.9	N.M.	N.M.	14.9
Laquinimod	0.0	0.0	3.5	6.9	N.M.	N.M.	14.9
Total	202.5	239.9	297.2	326.0	3.4	4.4	1.9
Spain							
Recombinant interferons	156.2	159.2	145.0	125.1	0.4	(1.9)	(2.9)
Interferon β-1b	55.7	50.3	37.1	29.0	(2.0)	(5.9)	(4.8)
Interferon β-1a (Avonex)	37.8	39.3	34.2	25.8	0.8	(2.8)	(5.5)
Interferon β-1a (Rebif)	62.7	69.6	73.7	70.3	2.1	1.2	(1.0)
Altered peptide ligands	11.4	15.6	19.6	19.2	6.5	4.7	(0.4)
Glatiramer acetate	11.4	15.6	16.0	13.3	6.5	0/5	(3.6)
M8P-8298	0.0	0.0	3.7	5.9	N.M.	N.M.	10.2
Chemotherapeutics	0.4	0.4	0.3	0.2	N.M.	(4.1)	(6.8)
Mitoxantrone	0.4	0.4	0.3	0.2	N.M.	(4.2)	(0.7)
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.1	1.8	7.2	10.0	79.1	31.8	6.8
Azathioprine	0.1	0.1	0.0	0.1	N.M.	(2.9)	N.M.
Teriflunomide	0.0	0.0	2.4	4.7	N.M.	N.M.	14.6
Cladribine	0.0	1.7	4.7	5.3	N.M.	22.3	2.1
Mycophenolate mofetil	0.0	0.0.	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	8.6	16.3	21.9	N.M.	13.7	6.1
Natalizumab	0.0	8.6	14.5	19.7	N.M.	11.1	6.3
Daclizumab	0.0	0.0	1.8	2.2	N.M.	N.M.	4.2
Corticosteroids	0.2	0.2	0.2	0.2	N.M.	N.M.	N.M.
Methylprednisolone	0.2	0.2	0.2	0.2	N.M.	N.M.	N.M.
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	19.6	28.9	N.M.	N.M.	8.0
FTY-720	0.0	0.0	16.0	21.8	N.M.	N.M.	6.4
BG-12	0.0	0.0	1.8	3.5	N.M.	N.M.	14.4
Laquinimod	0.0	0.0	1.8	3.5	N.M.	N.M.	14.4
Total	168.3	185.7	208.2	205.4	2.0	2.3	(0.3)

(continued)

Table 9-1 (cont.)

Sales of Drugs to Treat Multiple Sclerosis (All Populations) in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($ MM)				Growth (%/year) 2005-2010	Growth (%/year) 2010-2015	Growth (%/year) 2015-2020
	2005	2010	2015	2020			
United Kingdom							
Recombinant interferons	27.7	68.8	107.2	128.3	20.0	9.3	3.7
Interferon β-1b	6.7	12.1	10.7	11.6	12.5	(2.4)	1.5
Interferon β-1a (Avonex)	7.0	21.5	34.0	37.1	25.0	9.6	1.8
Interferon β-1a (Rebif)	13.9	35.2	62.5	79.6	20.4	12.2	5.0
Altered peptide ligands	13.2	26.9	36.3	35.8	15.3	6.2	(0.3)
Glatiramer acetate	13.2	26.9	29.7	25.3	15.3	2.0	(3.2)
MBP-8298	0.0	0.0	6.6	10.5	N.M.	N.M.	9.8
Chemotherapeutics	0.2	0.2	0.3	0.3	2.3	2.6	(1.1)
Mitoxantrone	0.2	0.2	0.3	0.2	2.1	2.5	(1.5)
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	N.M.	0.1	9.5	21.3	7.2	165.8	17.5
Azathioprine	N.M.	0.1	0.1	0.1	7.2	5.8	2.4
Teriflunomide	0.0	0.0	4.7	10.6	N.M.	N.M.	17.6
Cladribine	0.0	0.0	4.7	10.6	N.M.	N.M.	17.6
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	14.0	34.0	51.7	N.M.	19.4	8.7
Natalizumab	0.0	14.0	30.2	46.5	N.M.	16.6	9.0
Daclizumab	0.0	0.0	3.8	5.2	N.M.	N.M.	6.3
Corticosteroids	0.5	0.8	0.9	0.9	10.7	3.2	(0.2)
Methylprednisolone	0.5	0.8	0.9	0.9	10.7	3.2	(0.2)
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	28.9	50.3	N.M.	N.M.	11.8
FTY-720	0.0	0.0	21.3	33.5	N.M.	N.M.	9.5
BG-12	0.0	0.0	3.8	8.4	N.M.	N.M.	17.3
Laquinimod	0.0	0.0	3.8	8.4	N.M.	N.M.	17.3
Total	41.6	110.8	217.1	288.5	21.6	14.4	5.9
Japan							
Recombinant interferons	35.8	40.6	42.4	38.8	2.5	0.9	(1.7)
Interferon β-1b	35.8	34.0	25.6	18.7	(1.0)	(5.5)	(6.1)
Interferon β-1a (Avonex)	0.0	6.6	16.7	20.1	N.M.	20.6	3.8
Interferon β-1a (Rebif)	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Altered peptide ligands	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Glatiramer acetate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
MBP-8298	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Chemotherapeutics	0.1	0.0	0.0	0.0	N.M.	N.M.	N.M.
Mitoxantrone	0.1	0.0	0.0	0.0	N.M.	N.M.	N.M.
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.2	0.1	0.0	0.0	(7.0)	N.M.	N.M.
Azathioprine	0.2	0.1	0.0	0.0	(7.0)	N.M.	N.M.
Teriflunomide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.

(continued)

Table 9-1 (cont.)

Sales of Drugs to Treat Multiple Sclerosis (All Populations) in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($ MM)				Growth (%/year) 2005-2010	Growth (%/year) 2010-2015	Growth (%/year) 2015-2020
	2005	2010	2015	2020			
Cladribine	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	0.0	4.6	7.9	N.M.	N.M.	11.6
Natalizumab	0.0	0.0	4.6	7.9	N.M.	N.M.	11.6
Daclizumab	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Corticosteroids	0.3	0.3	0.2	0.2	(3.4)	(2.4)	(6.8)
Methylprednisolone	0.3	0.3	0.2	0.2	(3.4)	(2.4)	(6.8)
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	0.0	1.0	N.M.	N.M.	N.M.
FTY-720	0.0	0.0	0.0	1.0	N.M.	N.M.	N.M.
BG-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	36.4	41.0	47.3	48.0	2.4	2.9	0.3
Major-market total							
Recombinant interferons	2,942.2	3,096.2	2,768.7	2,497.1	1.0	(2.2)	(2.0)
Interferon β-1b	741.0	670.2	571.9	490.3	(2.0)	(3.1)	(3.0)
Interferon β-1a (Avonex)	1,359.2	1,345.3	992.9	780.7	(0.2)	(5.9)	(4.7)
Interferon β-1a (Rebif)	842.0	1,080.7	1,204.0	1,226.0	5.1	2.2	0.4
Altered peptide ligands	1,006.9	1,012.8	883.0	864.1	0.1	(2.7)	(0.4)
Glatiramer acetate	1,006.9	1,012.8	739.3	590.2	0.1	(6.1)	(4.4)
MBP-8298	0.0	0.0	143.7	273.8	N.M.	N.M.	13.8
Chemotherapeutics	46.5	32.1	19.8	13.1	(7.2)	(9.2)	(8.0)
Mitoxantrone	44.6	30.7	18.6	12.0	(7.2)	(9.6)	(8.3)
Cyclophosphamide	1.7	1.3	1.2	1.0	(5.7)	(1.9)	(3.7)
Methotrexate	0.2	0.0	0.0	0.0	(15.3)	N.M.	N.M.
Oral immunosuppressants	10.6	51.1	234.5	342.9	36.9	35.6	7.9
Azathioprine	5.7	4.1	3.8	3.4	(6.2)	(1.6)	(2.3)
Teriflunomide	0.0	0.0	64.0	133.0	N.M.	N.M.	15.7
Cladribine	0.0	41.8	161.7	203.3	N.M.	31.0	4.7
Mycophenolate mofetil	4.9	5.1	4.7	3.2	0.8	(1.0)	(8.1)
Monoclonal antibodies	21.9	358.2	573.4	740.6	74.9	9.9	5.3
Natalizumab	21.9	320.2	478.9	630.8	71.0	8.4	5.7
Daclizumab	0.0	38.0	94.4	109.7	N.M.	20.0	3.0
Corticosteroids	6.8	6.7	7.0	6.9	(0.3)	0.8	(0.3)
Methylprednisolone	6.7	6.6	6.9	6.8	(0.3)	0.8	(0.3)
Other corticosteroids	0.1	0.1	0.1	0.1	(0.2)	(0.2)	(1.2)
Oral immunomodulators	0.0	59.2	789.6	1,066.7	N.M.	67.9	6.2
FTY-720	0.0	59.2	693.5	869.4	N.M.	63.7	4.6
BG-12	0.0	0.0	48.0	98.7	N.M.	N.M.	15.5
Laquinimod	0.0	0.0	48.0	98.7	N.M.	N.M.	15.5
Total	4,035.0	4,616.4	5,276.0	5,531.3	2.7	2.7	0.9

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table 9-2

Sales of Drugs to Treat Relapsing-Remitting Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)	Growth (%/year)	Growth (%/year)
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
United States							
Recombinant interferons	1,356.1	1,354.4	1,071.3	875.1	N.M.	(4.6)	(4.0)
Interferon β-1b	149.9	107.2	79.2	61.5	(6.5)	(5.9)	(4.9)
Interferon β-1a (Avonex)	837.0	809.2	553.6	408.7	(0.7)	(7.3)	(5.9)
Interferon β-1a (Rebif)	369.2	438.0	438.5	404.9	3.5	N.M.	(1.6)
Altered peptide ligands	764.4	741.8	542.9	498.0	(0.6)	(6.1)	(1.7)
Glatiramer acetate	764.4	741.8	516.4	416.4	(0.6)	(7.0)	(4.2)
MBP-8298	0.0	0.0	26.5	81.7	N.M.	N.M.	25.2
Chemotherapeutics	18.4	11.2	7.4	5.0	(9.5)	(8.0)	(7.7)
Mitoxantrone	17.8	10.8	7.0	4.5	(9.5)	(8.3)	(8.3)
Cyclophosphamide	0.6	0.4	0.4	0.4	(7.8)	N.M.	0.5
Methotrexate	0.1	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	2.0	27.7	114.1	146.2	69.2	32.7	5.1
Azathioprine	2.0	1.0	1.1	1.1	(12.9)	1.9	0.5
Teriflunomide	0.0	0.0	28.2	58.0	N.M.	N.M.	15.5
Cladribine	0.0	26.6	84.7	87.1	N.M.	26.1	0.5
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	20.9	237.1	338.2	436.7	62.5	7.4	5.2
Natalizumab	20.9	204.8	304.0	401.6	57.8	8.2	5.7
Daclizumab	0.0	32.3	34.2	35.2	N.M.	1.1	0.5
Corticosteroids	1.8	1.9	2.0	2.1	1.1	1.0	0.5
Methylprednisolone	1.8	1.9	2.0	2.1	1.1	1.0	0.5
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	59.2	527.3	664.3	N.M.	54.9	4.7
FTY-720	0.0	59.2	470.8	548.2	N.M.	51.4	3.1
8G-12	0.0	0.0	28.2	58.0	N.M.	N.M.	15.5
Laquinimod	0.0	0.0	28.2	58.0	N.M.	N.M.	15.5
Total	2,163.6	2,433.3	2,603.3	2,627.5	2.4	1.4	0.2
Europe							
Recombinant interferons	918.1	970.1	874.7	785.9	1.1	(2.0)	(2.1)
Interferon β-1b	219.5	185.1	122.3	90.0	(3.4)	(8.0)	(5.7)
Interferon β-1a (Avonex)	312.2	331.4	267.4	222.4	1.2	(4.2)	(3.6)
Interferon β-1a (Rebif)	386.3	453.6	485.0	472.5	3.3	1.3	(0.5)
Altered peptide ligands	190.0	222.8	223.0	187.3	3.1	0.1	(3.4)
Glatiramer acetate	190.0	222.8	207.4	158.8	3.1	(1.3)	(5.2)
MBP-8298	0.0	0.0	15.7	28.6	N.M.	N.M.	12.7
Chemotherapeutics	2.7	2.1	1.6	1.4	(5.2)	(5.8)	(1.6)
Mitoxantrone	2.5	1.9	1.4	1.3	(5.3)	(6.1)	(1.1)
Cyclophosphamide	0.2	0.2	0.2	0.1	N.M.	N.M.	(6.4)
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	2.7	17.7	54.2	93.7	45.5	25.0	11.6
Azathioprine	2.1	1.8	1.6	1.2	(2.2)	(3.0)	(5.0)
Teriflunomide	0.0	0.0	19.8	40.6	N.M.	N.M.	15.5

(continued)

Table 9-2 (cont.)

Sales of Drugs to Treat Relapsing-Remitting Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)	Growth (%/year)	Growth (%/year)
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Cladribine	0.0	15.2	32.3	51.5	N.M.	16.3	9.8
Mycophenolate mofetil	0.7	0.7	0.5	0.4	N.M.	(6.5)	N.M.
Monoclonal antibodies	0.0	98.9	180.0	230.3	N.M.	12.7	5.0
Natalizumab	0.0	98.9	152.1	201.8	N.M.	9.0	5.8
Daclizumab	0.0	0.0	27.9	28.5	N.M.	N.M.	0.4
Corticosteroids	3.3	3.0	3.1	2.9	(1.7)	0.5	(1.1)
Methylprednisolone	3.2	2.9	3.0	2.8	(1.7)	0.5	(1.1)
Other corticosteroids	0.1	0.1	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	216.1	330.5	N.M.	N.M.	8.9
FTY-720	0.0	0.0	176.6	249.3	N.M.	N.M.	7.1
BG-12	0.0	0.0	20.0	40.6	N.M.	N.M.	15.5
Laquinimod	0.0	0.0	20.0	40.6	N.M.	N.M.	15.5
Total	1,116.8	1,313.7	1,552.8	1,632.1	3.3	3.4	1.0
France							
Recombinant interferons	185.9	186.0	156.4	138.3	N.M.	(3.4)	(2.4)
Interferon β-1b	27.1	19.9	13.1	10.6	(6.0)	(8.0)	(4.3)
Interferon β-1a (Avonex)	101.1	98.8	69.9	52.6	(0.5)	(6.7)	(5.5)
Interferon β-1a (Rebif)	57.7	67.3	73.3	75.1	3.1	1.7	0.5
Altered peptide ligands	33.1	49.5	47.5	39.5	8.4	(0.8)	(3.6)
Glatiramer acetate	33.1	49.5	44.7	33.8	8.4	(2.0)	(5.4)
MBP-8298	0.0	0.0	2.8	5.7	N.M.	N.M.	15.3
Chemotherapeutics	0.6	0.6	0.6	0.6	N.M.	N.M.	N.M.
Mitoxantrone	0.6	0.6	0.6	0.5	N.M.	N.M.	(1.7)
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	1.0	4.4	11.6	18.8	34.5	21.4	10.2
Azathioprine	0.3	0.3	0.3	0.2	N.M.	N.M.	(6.0)
Teriflunomide	0.0	0.0	3.6	7.3	N.M.	N.M.	15.3
Cladribine	0.0	3.4	7.2	11.0	N.M.	16.2	8.8
Mycophenolate mofetil	0.7	0.7	0.5	0.4	N.M.	(6.5)	N.M.
Monoclonal antibodies	0.0	21.1	34.5	40.7	N.M.	10.3	3.4
Natalizumab	0.0	21.1	27.6	33.7	N.M.	5.5	4.1
Daclizumab	0.0	0.0	6.9	7.0	N.M.	N.M.	0.3
Corticosteroids	0.7	0.7	0.7	0.7	N.M.	N.M.	N.M.
Methylprednisolone	0.7	0.6	0.7	0.7	(3.0)	3.1	(0.2)
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	(0.1)
Oral immunomodulators	0.0	0.0	47.6	70.7	N.M.	N.M.	8.2
FTY-720	0.0	0.0	40.4	56.0	N.M.	N.M.	6.8
BG-12	0.0	0.0	3.6	7.3	N.M.	N.M.	15.3
Laquinimod	0.0	0.0	3.6	7.3	N.M.	N.M.	15.3
Total	221.2	262.2	298.9	309.3	3.5	2.7	0.7

(continued)

Table 9-2 (cont.)

Sales of Drugs to Treat Relapsing-Remitting Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)	Growth (%/year)	Growth (%/year)
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Germany							
Recombinant interferons	419.6	432.8	365.8	315.9	0.6	(3.3)	(2.9)
Interferon β-1b	124.9	105.7	70.7	51.2	(3.3)	(7.7)	(6.3)
Interferon β-1a (Avonex)	119.6	124.5	95.8	82.1	0.8	(5.1)	(3.1)
Interferon β-1a (Rebif)	175.1	202.6	199.2	182.7	3.0	(0.3)	(1.7)
Altered peptide ligands	112.8	104.3	100.6	80.9	(1.6)	(0.7)	(4.3)
Glatiramer acetate	112.8	104.3	95.3	70.1	(1.6)	(1.8)	(6.0)
MBP-8298	0.0	0.0	5.3	10.8	N.M.	N.M.	15.1
Chemotherapeutics	1.5	0.9	0.5	0.4	(9.7)	(11.1)	(3.4)
Mitoxantrone	1.4	0.9	0.4	0.4	(8.5)	(15.0)	(1.5)
Cyclophosphamide	0.1	0.1	0.1	0.0	N.M.	N.M.	(15.1)
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	1.4	7.8	22.4	36.8	41.0	23.5	10.4
Azathioprine	1.4	1.2	1.0	0.8	(3.0)	(3.6)	(5.4)
Teriflunomide	0.0	0.0	7.1	14.4	N.M.	N.M.	15.1
Cladribine	0.0	6.6	14.3	21.6	N.M.	16.7	8.7
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	40.8	65.7	77.5	N.M.	10.0	3.4
Natalizumab	0.0	40.8	54.8	66.5	N.M.	6.1	3.9
Daclizumab	0.0	0.0	10.9	11.1	N.M.	N.M.	0.2
Corticosteroids	1.7	1.2	1.2	1.1	(6.7)	N.M.	(1.4)
Methylprednisolone	1.6	1.2	1.2	1.1	(5.6)	N.M.	(1.4)
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	87.5	132.5	N.M.	N.M.	8.7
FTY-720	0.0	0.0	73.2	103.7	N.M.	N.M.	7.2
BG-12	0.0	0.0	7.1	14.4	N.M.	N.M.	15.1
Laquinimod	0.0	0.0	7.1	14.4	N.M.	N.M.	15.1
Total	536.9	587.9	643.7	645.1	1.8	1.8	0.0
Italy							
Recombinant interferons	162.2	167.0	153.8	136.2	0.6	(1.6)	(2.4)
Interferon β-1b	24.7	18.5	12.5	8.3	(5.6)	(7.5)	(7.8)
Interferon β-1a (Avonex)	51.0	54.5	43.8	35.7	1.3	(4.3)	(4.0)
Interferon β-1a (Rebif)	86.5	94.0	97.6	92.1	1.7	0.8	(1.1)
Altered peptide ligands	20.5	27.1	25.8	23.1	5.7	(1.0)	(2.1)
Glatiramer acetate	20.5	27.1	23.0	17.7	5.7	(3.2)	(5.2)
MBP-8298	0.0	0.0	2.7	5.5	N.M.	N.M.	14.9
Chemotherapeutics	0.4	0.3	0.1	0.1	(5.6)	(19.7)	(0.2)
Mitoxantrone	0.4	0.3	0.1	0.1	(5.6)	(19.7)	(0.2)
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.3	3.7	7.1	14.0	65.3	13.9	14.5
Azathioprine	0.3	0.2	0.2	0.1	(7.8)	N.M.	(6.0)
Teriflunomide	0.0	0.0	3.5	6.9	N.M.	N.M.	14.9

(continued)

Table 9-2 (cont.)

Sales of Drugs to Treat Relapsing-Remitting Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)	Growth (%/year)	Growth (%/year)
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Cladribine	0.0	3.4	3.5	6.9	N.M.	0.6	14.9
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	15.8	32.3	42.9	N.M.	15.4	5.9
Natalizumab	0.0	15.8	26.6	37.2	N.M.	11.0	7.0
Daclizumab	0.0	0.0	5.7	5.7	N.M.	N.M.	0.0
Corticosteroids	0.4	0.4	0.4	0.4	N.M.	N.M.	N.M.
Methylprednisolone	0.4	0.4	0.4	0.4	N.M.	N.M.	N.M.
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	35.6	53.2	N.M.	N.M.	8.4
FTY-720	0.0	0.0	28.6	39.4	N.M.	N.M.	6.6
BG-12	0.0	0.0	3.5	6.9	N.M.	N.M.	14.9
Laquinimod	0.0	0.0	3.5	6.9	N.M.	N.M.	14.9
Total	183.8	214.3	255.1	270.0	3.1	3.5	1.1
Spain							
Recombinant interferons	126.7	127.4	110.6	92.2	0.1	(2.8)	(3.6)
Interferon β-1b	37.7	32.5	19.4	13.7	(2.9)	(9.8)	(6.7)
Interferon β-1a (Avonex)	34.5	35.5	29.6	21.6	(0.6)	(3.6)	(6.1)
Interferon β-1a (Rebif)	54.6	59.4	61.7	56.9	1.7	0.7	(1.6)
Altered peptide ligands	10.7	14.8	16.6	15.4	6.7	2.3	(1.6)
Glatiramer acetate	10.7	14.8	15.2	12.6	6.7	0.5	(3.7)
M8P-8298	0.0	0.0	1.4	2.8	N.M.	N.M.	14.4
Chemotherapeutics	0.1	0.1	0.1	0.1	N.M.	N.M.	(2.2)
Mitoxantrone	0.1	0.1	0.1	0.1	N.M.	N.M.	(2.3)
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.1	1.8	5.5	7.1	92.0	25.1	5.5
Azathioprine	0.1	0.1	0,1	0.0	N.M.	N.M.	(1.2)
Teriflunomide	0.0	0.0	1.8	3.5	N.M.	N.M.	14.4
Cladribine	0.0	1.7	3.6	3.6	N.M.	15.8	(0.4)
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	8.0	15.2	20.4	N.M.	13.8	6.0
Natalizumab	0.0	8.0	13.9	19.1	N.M.	11.7	6.6
Daclizumab	0.0	0.0	1.4	1.3	N.M.	N.M.	(1.9)
Corticosteroids	0.1	0.1	0.1	0.1	N.M.	N.M.	N.M.
Methylprednisolone	0.1	0.1	0.1	0.1	N.M.	N.M.	N.M.
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	18.5	27.1	N.M.	N.M.	8.0
FTY-720	0.0	0.0	14.9	20.0	N.M.	N.M.	6.2
8G-12	0.0	0.0	1.8	3.5	N.M.	N.M.	14.4
Laquinimod	0.0	0.0	1.8	3.5	N.M.	N.M.	14.4
Total	137.7	152.2	166.6	162.4	2.0	1.8	0.5

(continued)

Table 9-2 (cont.)

Sales of Drugs to Treat Relapsing-Remitting Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)	Growth (%/year)	Growth (%/year)
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
United Kingdom							
Recombinant interferons	23.6	56.9	88.1	103.3	19.2	9.1	3.2
Interferon β-1b	5.1	8.5	6.5	7.2	10.8	(5.2)	2.0
Interferon β-1a (Avonex)	6.1	18.2	28.4	30.5	24.4	9.3	1.4
Interferon β-1a (Rebif)	12.4	30.2	53.2	65.6	19.5	12.0	4.3
Altered peptide ligands	12.9	26.1	32.5	28.5	15.1	4.5	(2.6)
Glatiramer acetate	12.9	26.1	29.2	24.7	15.1	2.3	(3.3)
MBP-829B	0.0	0.0	3.4	3.7	N.M.	N.M.	2.1
Chemotherapeutics	0.2	0.2	0.2	0.2	N.M.	N.M.	N.M.
Mitoxantrone	0.2	0.1	0.2	0.2	(12.9)	14.9	1.7
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.0	0.1	7.7	16.9	N.M.	138.4	17.2
Azathioprine	0.0	0.1	0.1	0.1	N.M.	N.M.	N.M.
Teriflunomide	0.0	0.0	3.8	8.4	N.M.	N.M.	17.3
Cladribine	0.0	0.0	3.8	8.4	N.M.	N.M.	17.3
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	13.3	32.3	48.8	N.M.	19.4	8.6
Natalizumab	0.0	13.3	29.2	45.3	N.M.	17.0	9.2
Daclizumab	0.0	0.0	3.1	3.4	N.M.	N.M.	2.1
Corticosteroids	0.4	0.6	0.6	0.6	8.4	N.M.	N.M.
Methylprednisolone	0.4	0.6	0.6	0.6	8.4	N.M.	N.M.
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	27.0	47.0	N.M.	N.M.	11.7
FTY-720	0.0	0.0	19.4	30.2	N.M.	N.M.	9.2
BG-12	0.0	0.0	3.8	8.4	N.M.	N.M.	17.3
Laquinimod	0.0	0.0	3.8	8.4	N.M.	N.M.	17.3
Total	37.0	97.1	188.4	245.3	21.3	14.2	5.4
Japan							
Recombinant interferons	32.4	36.4	37.4	34.4	2.3	0.5	(1.7)
Interferon β-1b	32.4	30.2	21.6	15.5	(1.4)	(6.5)	(6.4)
Interferon β-1a (Avonex)	0.0	6.2	15.8	18.9	N.M.	20.6	3.5
Interferon β-1a (Rebif)	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Altered peptide ligands	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Glatiramer acetate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
MBP-8298	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Chemotherapeutics	0.1	0.0	0.0	0.0	N.M.	N.M.	N.M.
Mitoxantrone	0.1	0.0	0.0	0.0	N.M.	N.M.	N.M.
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.1	0.1	0.1	0.0	N.M.	N.M.	(16.2)
Azathioprine	0.1	0.1	0.1	0.0	N.M.	N.M.	(16.2)
Teriflunomide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.

(continued)

Table 9-2 (cont.)

Sales of Drugs to Treat Relapsing-Remitting Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)	Growth (%/year)	Growth (%/year)
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Cladribine	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	0.0	4.4	7.8	N.M.	N.M.	11.9
Natalizumab	0.0	0.0	4.4	7.8	N.M.	N.M.	11.9
Daclizumab	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Corticosteroids	0.3	0.2	0.2	0.2	(7.8)	N.M.	N.M.
Methylprednisolone	0.3	0.2	0.2	0.2	(7.8)	N.M.	N.M.
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	0.0	0.9	N.M.	N.M.	N.M.
FTY-720	0.0	0.0	0.0	0.9	N.M.	N.M.	N.M.
BG-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	32.9	36.8	42.2	43.2	2.2	2.8	0.5
Major-market total							
Recombinant interferons	2,306.6	2,360.8	1,983.4	1,695.4	0.5	(3.4)	(3.1)
Interferon β-1b	401.8	322.4	223.0	168.0	(4.3)	(7.1)	(5.5)
Interferon β-1a (Avonex)	1,149.6	1,146.8	836.9	650.0	N.M.	(6.1)	(4.9)
Interferon β-1a (Rebif)	755.6	891.6	923.5	877.4	3.4	0.7	(1.1)
Altered peptide ligands	954.4	963.7	766.0	685.3	0.2	(4.5)	(2.2)
Glatiramer acetate	954.4	963.7	723.8	575.1	0.2	(5.6)	(4.5)
MBP-8298	0.0	0.0	42.2	110.2	N.M.	N.M.	21.2
Chemotherapeutics	21.2	13.3	9.0	6.4	(8.9)	(7.5)	(6.5)
Mitoxantrone	20.3	12.7	8.4	5.9	(8.9)	(7.9)	(7.0)
Cyclophosphamide	0.8	0.6	0.6	0.6	(5.6)	N.M.	N.M.
Methotrexate	0.1	0.0	0.0	0.0	(32.6)	N.M.	N.M.
Oral immunosuppressants	4.8	45.5	168.4	240.0	56.6	29.9	7.3
Azathioprine	4.2	3.0	2.8	2.4	(6.5)	(1.3)	(2.8)
Teriflunomide	0.0	0.0	48.0	98.6	N.M.	N.M.	15.5
Cladribine	0.0	41.8	117.1	138.5	N.M.	22.8	3.4
Mycophenolate mofetil	0.7	0.7	0.5	0.4	N.M.	(6.5)	N.M.
Monoclonal antibodies	20.9	336.0	522.7	674.8	74.3	9.2	5.2
Natalizumab	20.9	303.8	460.5	611.2	70.8	8.7	5.8
Daclizumab	0.0	32.3	62.1	63.6	N.M.	14.0	0.5
Corticosteroids	5.4	5.1	5.3	5.1	0.8	0.6	(0.6)
Methylprednisolone	5.3	5.1	5.2	5.1	(0.8)	0.6	(0.6)
Other corticosteroids	0.1	0.1	0.1	0.1	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	59.2	743.5	995.7	N.M.	65.9	6.0
FTY-720	0.0	59.2	647.4	798.4	N.M.	61.3	4.3
BG-12	0.0	0.0	48.0	98.7	N.M.	N.M.	15.5
Laquinimod	0.0	0.0	48.0	98.7	N.M.	N.M.	15.5
Total	3,313.3	3,783.8	4,198.3	4,302.8	2.7	2.1	0.5

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table 9-3

Sales of Drugs to Treat Chronic-Progressive Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)		
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
United States							
Recombinant interferons	489.1	550.1	565.0	562.4	2.4	0.5	(0.1)
IFN-β-1b	249.5	253.6	252.8	232.0	0.3	(0.1)	(1.7)
IFN-β-1a (Avonex)	187.9	167.0	114.5	86.3	(2.3)	(7.3)	(5.5)
IFN-β-1a (Rebif)	51.8	129.5	197.7	244.2	20.1	8.8	4.3
Altered peptide ligands	43.4	41.6	85.2	131.0	(0.8)	15.4	9.0
Glatiramer acetate	43.4	41.6	7.9	7.8	(0.8)	(28.3)	0.0
MBP-8298	0.0	0.0	77.3	123.1	N.M.	N.M.	9.7
Chemotherapeutics	20.2	14.0	6.9	3.8	(7.1)	(13.2)	(11.3)
Mitoxantrone	19.3	13.4	6.4	3.4	(7.0)	(13.7)	(11.8)
Cyclophosphamide	0.8	0.6	0.5	0.3	(5.6)	(3.6)	(6.7)
Methotrexate	0.1	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	3.5	3.3	44.9	68.3	(1.2)	68.6	8.8
Azathioprine	1.0	0.7	0.8	0.9	(6.9)	2.7	1.2
Teriflunomide	0.0	0.0	10.3	21.9	N.M.	N.M.	16.2
Cladribine	0.0	0.0	30.9	43.8	N.M.	N.M.	7.2
Mycophenolate mofetil	2.5	2.5	2.8	1.8	N.M.	2.3	N.M.
Monoclonal antibodies	1.0	16.9	37.2	46.1	76.0	17.1	4.4
Natalizumab	1.0	11.2	12.2	12.9	62.1	1.7	1.2
Daclizumab	0.0	5.7	25.0	33.1	N.M.	34.4	5.8
Corticosteroids	0.6	0.7	0.7	0.7	3.1	N.M.	0.4
Methylprednisolone	0.6	0.6	0.7	0.7	N.M.	3.1	0.4
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	1.2
Oral immunomodulators	0.0	0.0	34.4	51.7	N.M.	N.M.	8.5
FTY-720	0.0	0.0	34.4	51.7	N.M.	N.M.	8.5
BG-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	557.8	626.5	774.2	863.8	2.4	4.3	2.2
Europe							
Recombinant interferons	143.1	181.1	215.4	234/9	4.8	3.5	1.7
IFN-β-1b	86.3	90.3	92.0	87.2	0.9	0.4	(1.1)
IFN-β-1a (Avonex)	22.1	31.2	40.7	43.2	7.1	5.5	1.2
IFN-β-1a (Rebif)	34.6	59.6	82.8	104.4	11.5	6.B	4.8
Altered peptide ligands	9.2	7.5	31.8	47.8	(4.0)	33.5	8.5
Glatiramer acetate	9.2	7.5	7.6	7.2	(4.0)	0.3	(1.0)
MBP-829B	0.0	0.0	24.2	40.5	N.M.	N.M.	12.3
Chemotherapeutics	5.1	4.7	3.8	2.8	(1.6)	(4.2)	(6.0)
Mitoxantrone	4.9	4.5	3.7	2.7	(1.7)	(3.8)	(6.0)
Cyclophosphamide	0.2	0.1	0.1	0.1	(12.9)	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.

(continued)

Table 9-3 (cont.)

Sales of Drugs to Treat Chronic-Progressive Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)		
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Oral immunosuppressants	2.3	2.3	21.2	34.7	N.M.	55.9	10.4
Azathioprine	0.5	0.4	0.2	0.1	(4.4)	(12.9)	(8.7)
Teriflunomide	0.0	0.0	5.7	12.4	N.M.	N.M.	16.9
Cladribine	0.0	0.0	13.7	21.0	N.M.	N.M.	8.9
Mycophenolate mofetil	1.8	1.9	1.5	1.1	1.1	(4.6)	N.M.
Monoclonal antibodies	0.0	5.2	13.4	19.6	N.M.	20.8	7.9
Natalizumab	0.0	5.2	6.0	6.6	N.M.	2.9	1.7
Daclizumab	0.0	0.0	7.3	13.0	N.M.	N.M.	12.1
Corticosteroids	0.8	0.9	1.0	1.1	2.4	2.1	1.2
Methylprednisolone	0.8	0.9	1.0	1.1	2.4	2.1	1.9
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	11.7	19.2	N.M.	N.M.	10.3
FTY-720	0.0	0.0	11.7	19.2	N.M.	N.M.	10.3
BG-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	160.4	201.7	298.3	360.0	4.7	8.1	3.8
France							
Recombinant interferons	37.1	39.0	40.8	40.3	1.0	0.9	(0.3)
IFN-β-1b	23.5	21.5	19.8	17.3	(1.8)	(1.6)	(2.7)
IFN-β-1a (Avonex)	6.1	6.2	6.0	5.0	0.3	(0.7)	(3.9)
IFN-β-1a (Rebif)	7.5	11.3	14.9	18.1	8.5	5.7	3.8
Altered peptide ligands	1.3	0.7	5.4	8.0	(11.6)	50.5	8.0
Glatiramer acetate	1.3	0.7	0.7	0.7	(11.6)	N.M.	N.M.
MBP-8298	0.0	0.0	4.7	7.3	N.M.	N.M.	9.2
Chemotherapeutics	1.4	1.2	0.9	0.6	(3.0)	(5.6)	(7.4)
Mitoxantrone	1.3	1.1	0.9	0.6	(3.3)	(3.9)	0.1
Cyclophosphamide	0.1	0.1	0.0	0.0	N.M.	N.M.	(5.3)
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	1.9	2.0	5.5	7.3	1.0	22.4	5.7
Azathioprine	0.1	0.1	0.0	0.0	N.M.	N.M.	N.M.
Teriflunomide	0.0	0.0	1.0	2.1	N.M.	N.M.	15.7
Cladribine	0.0	0.0	3.0	4.2	N.M.	N.M.	6.7
Mycophenolate mofetil	1.8	1.9	1.5	1.1	1.1	(4.6)	(6.0)
Monoclonal antibodies	0.0	1.0	3.0	4.1	N.M.	24.6	6.5
Natalizumab	0.0	1.0	1.1	1.1	N.M.	1.9	0.7
Daclizumab	0.0	0.0	1.9	3.0	N.M.	N.M.	9.2
Corticosteroids	0.2	0.2	0.2	0.2	N.M.	N.M.	N.M.
Methylprednisolone	0.2	0.2	0.2	0.2	N.M.	N.M.	N.M.
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.

(continued)

Table 9-3 (cont.)

Sales of Drugs to Treat Chronic-Progressive Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)		
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Oral immunomodulators	0.0	0.0	2.0	3.2	N.M.	N.M.	9.2
FTY-720	0.0	0.0	2.0	3.2	N.M.	N.M.	9.2
BG-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	41.7	43.9	57.8	63.8	1.0	5.7	2.0
Germany							
Recombinant interferons	55.5	75.2	91.0	100.2	6.3	3.9	2.0
IFN-β-1b	29.3	32.0	34.2	34.5	1.8	1.3	0.2
IFN-β-1a (Avonex)	10.9	15.8	21.1	23.1	7.7	6.0	1.9
IFN-β-1a (Rebif)	15.3	27.4	35.8	42.7	12.4	5.5	3.6
Altered peptide ligands	5.7	4.3	15.1	21.2	(5.5)	28.6	7.0
Glatiramer acetate	5.7	4.3	5.0	4.7	(5.5)	3.1	(1.0)
M8P-8298	0.0	0.0	10.1	16.4	N.M.	N.M.	10.3
Chemotherapeutics	3.0	2.8	2.3	1.7	(1.4)	(3.9)	(5.4)
Mitoxantrone	2.9	2.7	2.3	1.7	(1.4)	(3.2)	0.1
Cyclophosphamide	0.1	0.1	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.3	0.3	9.1	14.7	N.M.	97.9	10.0
Azathioprine	0.3	0.3	0.2	0.0	N.M.	(7.8)	(11.5)
Teriflunomide	0.0	0.0	2.2	4.9	N.M.	N.M.	16.8
Cladribine	0.0	0.0	6.7	9.7	N.M.	N.M.	7.7
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	2.0	5.8	8.2	N.M.	23.7	7.1
Natalizumab	0.0	2.0	2.4	2.6	N.M.	3.7	1.7
Daclizumab	0.0	0.0	3.4	5.6	N.M.	N.M.	10.3
Corticosteroids	0.4	0.4	0.4	0.4	N.M.	N.M.	N.M.
Methylprednisolone	0.4	0.4	0.4	0.4	N.M.	N.M.	N.M.
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	4.6	7.5	N.M.	N.M.	10.3
FTY-720	0.0	0.0	4.6	7.5	N.M.	N.M.	10.3
BG-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	64.9	85.0	128.3	153.9	5.5	8.6	3.7
Italy							
Recombinant interferons	17.0	23.2	30.1	36.2	6.4	5.3	3.8
IFN-β-1b	13.9	15.5	16.2	15.7	2.2	0.9	(0.6)
IFN-β-1a (Avonex)	0.8	2.0	3.3	4.3	20.1	10.5	5.4
IFN-β-1a (Rebif)	2.2	5.7	10.7	16.3	21.0	13.4	8.7
Altered peptide ligands	1.1	1.0	4.5	7.5	(1.9)	35.1	10.7

(continued)

Table 9-3 (cont.)

Sales of Drugs to Treat Chronic-Progressive Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)		
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Glatiramer acetate	1.1	1.0	0.6	0.6	(1.9)	(9.7)	0.1
MBP-8298	0.0	0.0	3.9	6.9	N.M.	N.M.	11.8
Chemotherapeutics	0.3	0.4	0.3	0.3	5.9	(5.6)	(4.1)
Mitoxantrone	0.3	0.3	0.3	0.2	N.M.	N.M.	(4.1)
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.0	0.0	3.0	5.4	N.M.	N.M.	12.7
Azathioprine	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Teriflunomide	0.0	0.0	1.0	2.2	N.M.	N.M.	16.9
Cladribine	0.0	0.0	2.0	3.3	N.M.	N.M.	10.4
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	0.9	1.9	3.0	N.M.	16.1	9.4
Natalizumab	0.0	0.9	1.1	1.2	N.M.	4.1	1.8
Daclizumab	0.0	0.0	0.8	1.8	N.M.	N.M.	16.9
Corticosteroids	0.1	0.1	0.1	0.2	N.M.	N.M.	1.5
Methylprednisolone	0.1	0.1	0.1	0.2	N.M.	N.M.	1.5
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	2.1	3.4	N.M.	N.M.	10.4
FTY-720	0.0	0.0	2.1	3.4	N.M.	N.M.	10.4
8G-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	18.6	25.6	42.0	56.0	6.6	10.4	5.9
Spain							
Recombinant interferons	29.4	31.8	34.3	32.9	1.6	1.5	(0.9)
IFN-β-1b	18.0	17.8	17.7	15.4	(0.2)	(0.1)	(2.8)
IFN-β-1a (Avonex)	3.3	3.9	4.6	4.1	3.4	3.4	(2.1)
IFN-β-1a (Rebif)	8.1	10.2	12.0	13.4	4.7	3.3	2.1
Altered peptide ligands	0.7	0.8	3.0	3.9	2.7	30.3	5.1
Glatiramer acetate	0.7	0.8	0.8	0.7	2.7	N.M.	(1.5)
MBP-8298	0.0	0.0	2.2	3.1	N.M.	N.M.	7.1
Chemotherapeutics	0.4	0.3	0.2	0.1	(5.6)	(7.8)	(9.3)
Mitoxantrone	0.4	0.3	0.2	0.1	(5.6)	(7.8)	(9.4)
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.0	0.0	1.7	2.8	N.M.	N.M.	10.8
Azathioprine	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Teriflunomide	0.0	0.0	0.6	1.1	N.M.	N.M.	15.1
Cladribine	0.0	0.0	1.1	1.7	N.M.	N.M.	8.7
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.

(continued)

Table 9-3 (cont.)

Sales of Drugs to Treat Chronic-Progressive Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)		
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Monoclonal antibodies	0.0	0.6	1.0	1.4	N.M.	10.8	7.3
Natalizumab	0.0	0.6	0.6	0.6	N.M.	N.M.	0.2
Daclizumab	0.0	0.0	0.4	0.8	N.M.	N.M.	15.1
Corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methylprednisolone	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	1.2	1.8	N.M.	N.M.	8.6
FTY-720	0.0	0.0	1.2	1.7	N.M.	N.M.	8.6
BG-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	30.6	33.5	41.5	43.0	1.8	4.4	0.7
United Kingdom							
Recombinant interferons	4.1	11.9	19.2	25.0	23.8	10.0	5.4
IFN-β-1b	1.6	3.5	4.2	4.3	16.9	3.7	0.8
IFN-β-1a (Avonex)	1.0	3.3	5.7	6.7	27.0	11.6	3.4
IFN-β-1a (Rebif)	1.5	5.1	9.3	14.0	27.7	12.8	8.4
Altered peptide ligands	0.3	0.8	3.8	7.3	21.7	36.6	14.1
Glatiramer acetate	0.3	0.8	0.5	0.5	21.7	(9.0)	(0.1)
MBP-8298	0.0	0.0	3.2	6.7	N.M.	N.M.	15.9
Chemotherapeutics	0.1	0.1	0.1	0.0	N.M.	N.M.	(8.8)
Mitoxantrone	0.0	0.1	0.1	0.0	N.M.	N.M.	(10.1)
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.0	0.0	1.8	4.4	N.M.	N.M.	19.0
Azathioprine	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Teriflunomide	0.0	0.0	0.9	2.2	N.M.	N.M.	19.1
Cladribine	0.0	0.0	0.9	2.2	N.M.	N.M.	19.1
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	0.7	1.7	2.9	N.M.	19.4	11.5
Natalizumab	0.0	0.7	1.0	1.1	N.M.	7.4	3.7
Daclizumab	0.0	0.0	0.7	1.8	N.M.	N.M.	19.1
Corticosteroids	0.1	0.2	0.3	0.3	14.9	8.4	N.M.
Methylprednisolone	0.1	0.2	0.3	0.3	14.9	8.4	N.M.
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	1.9	3.3	N.M.	N.M.	12.5
FTY-720	0.0	0.0	1.9	3.3	N.M.	N.M.	12.5
BG-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	4.6	13.7	28.7	43.3	24.4	15.9	8.6

(continued)

Table 9-3 (cont.)

Sales of Drugs to Treat Chronic-Progressive Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)		
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Japan							
Recombinant interferons	3.4	4.2	4.9	4.5	4.3	3.1	(1.9)
IFN-β-1b	3.4	3.8	4.0	3.2	2.2	1.0	(4.6)
IFN-β-1a (Avonex)	0.0	0.4	0.9	1.3	N.M.	17.6	7.7
IFN-β-1a (Rebif)	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Altered peptide ligands	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Glatiramer acetate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
MBP-8298	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Chemotherapeutics	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Mitoxantrone	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Cyclophosphamide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methotrexate	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Azathioprine	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Teriflunomide	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Cladribine	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Mycophenolate mofetil	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Monoclonal antibodies	0.0	0.0	0.1	0.2	N.M.	N.M.	1.5
Natalizumab	0.0	0.0	0.1	0.2	N.M.	N.M.	1.5
Daclizumab	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Methylprednisolone	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	0.0	0.1	N.M.	N.M.	N.M.
FTY-720	0.0	0.0	0.0	0.1	N.M.	N.M.	N.M.
8G-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	3.5	4.3	5.1	5.0	4.2	3.5	(1.3)
Major-market total							
Recombinant interferons	635.6	735.4	785.3	801.7	3.0	1.3	0.4
IFN-β-1b	339.2	347.8	348.8	322.4	0.5	0.1	(1.6)
IFN-β-1a (Avonex)	210.1	198.5	156.0	130.7	(1.1)	(4.7)	(3.5)
IFN-β-1a (Rebif)	86.4	189.1	280.5	348.6	17.0	8.2	4.4
Altered peptide ligands	52.5	49.1	117.0	178.7	(1.3)	19.0	8.8
Glatiramer acetate	52.5	49.1	15.5	15.1	(1.3)	(20.6)	0.5
MBP-8298	0.0	0.0	101.5	163.7	N.M.	N.M.	10.0
Chemotherapeutics	25.3	18.7	10.8	6.6	(5.9)	(10.4)	(9.2)
Mitoxantrone	24.3	18.0	10.1	6.2	(5.8)	(10.9)	(9.5)
Cyclophosphamide	1.0	0.7	0.6	0.4	(6.9)	(3.0)	(6.6)

(continued)

Table 9-3 (cont.)

Sales of Drugs to Treat Chronic-Progressive Multiple Sclerosis in the Major Pharmaceutical Markets, 2005-2020 (millions of 2005 U.S. dollars)

	Sales of Major Drugs/Classes ($MM)				Growth (%/year)		
	2005	2010	2015	2020	2005-2010	2010-2015	2015-2020
Methotrexate	0.1	0.1	0.1	0.0	N.M.	N.M.	N.M.
Oral immunosuppressants	5.8	5.6	66.1	102.9	(0.7)	63.8	9.3
Azathioprine	1.5	1.1	1.1	1.0	(6.0)	N.M.	(0.8)
Teriflunomide	0.0	0.0	16.0	34.3	N.M.	N.M.	16.5
Cladribine	0.0	0.0	44.7	64.8	N.M.	N.M.	7.7
Mycophenolate mofetil	4.3	4.4	4.3	2.8	0.5	(0.5)	N.M.
Monoclonal antibodies	1.0	22.1	50.7	65.8	85.7	18.1	5.4
Natalizumab	1.0	16.4	18.4	19.7	75.0	2.3	1.4
Daclizumab	0.0	5.7	32.3	146.1	N.M.	41.5	7.4
Corticosteroids	1.5	1.6	1.7	1.8	1.3	1.2	1.1
Methylprednisolone	1.5	1.6	1.7	1.8	1.3	1.2	1.1
Other corticosteroids	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Oral immunomodulators	0.0	0.0	46.1	71.0	N.M.	N.M.	9.0
FTY-720	0.0	0.0	46.1	71.0	N.M.	N.M.	9.0
BG-12	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Laquinimod	0.0	0.0	0.0	0.0	N.M.	N.M.	N.M.
Total	721.8	832.6	1,077.6	1,228.5	2.9	5.3	2.7

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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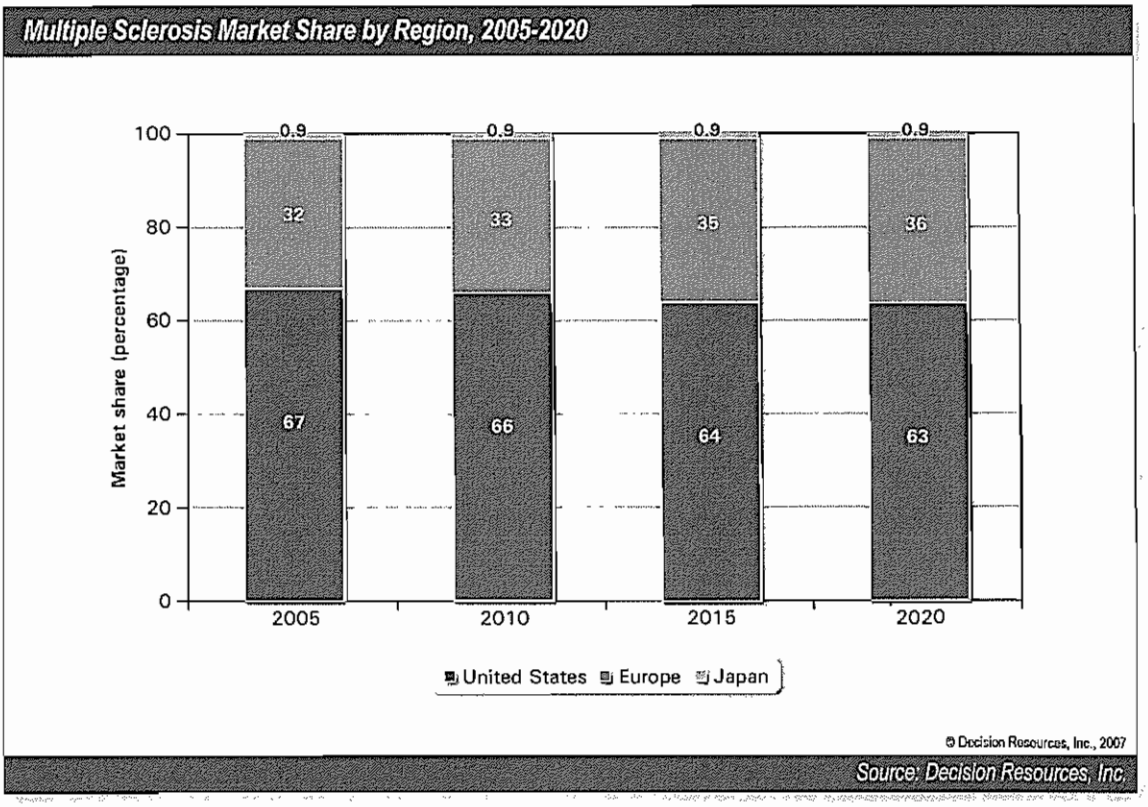
Source: Decision Resources, Inc.

The safety risks associated with natalizumab (Biogen Idec/Elan's Tysabri) have radically altered the landscape of the MS market. Although natalizumab returned to the U.S. market in July 2006 and was launched in Europe at the same time, its significant safety risks will keep it from garnering much patient share. Nevertheless, because of its high price point, we expect that natalizumab sales will represent 11% of major-market sales in 2020.

Over our study period, we expect little use of combination therapies; the cases of progressive multifocal leukoencephalopathy (PML) that developed with natalizumab/IFN-β-1a (Biogen Idec's Avonex) combination use have made physicians, patients, and regulatory agencies very wary of combination therapy. Currently, the most frequent combination therapy consists of IFN-βs in combination with corticosteroids or pulsed immunosuppressants for aggressive RR-MS and those SP-MS patients who are experiencing relapses. Although experts interviewed are concerned about combining immunomodulatory agents, most note that they would be willing to use disease-modifying therapies in combination with neuroprotective or remyelinating agents when they become available. One expert explains, "This is the new therapy strategy, combination therapy by using immune suppression or immune modulation and neuroprotection because MS is not

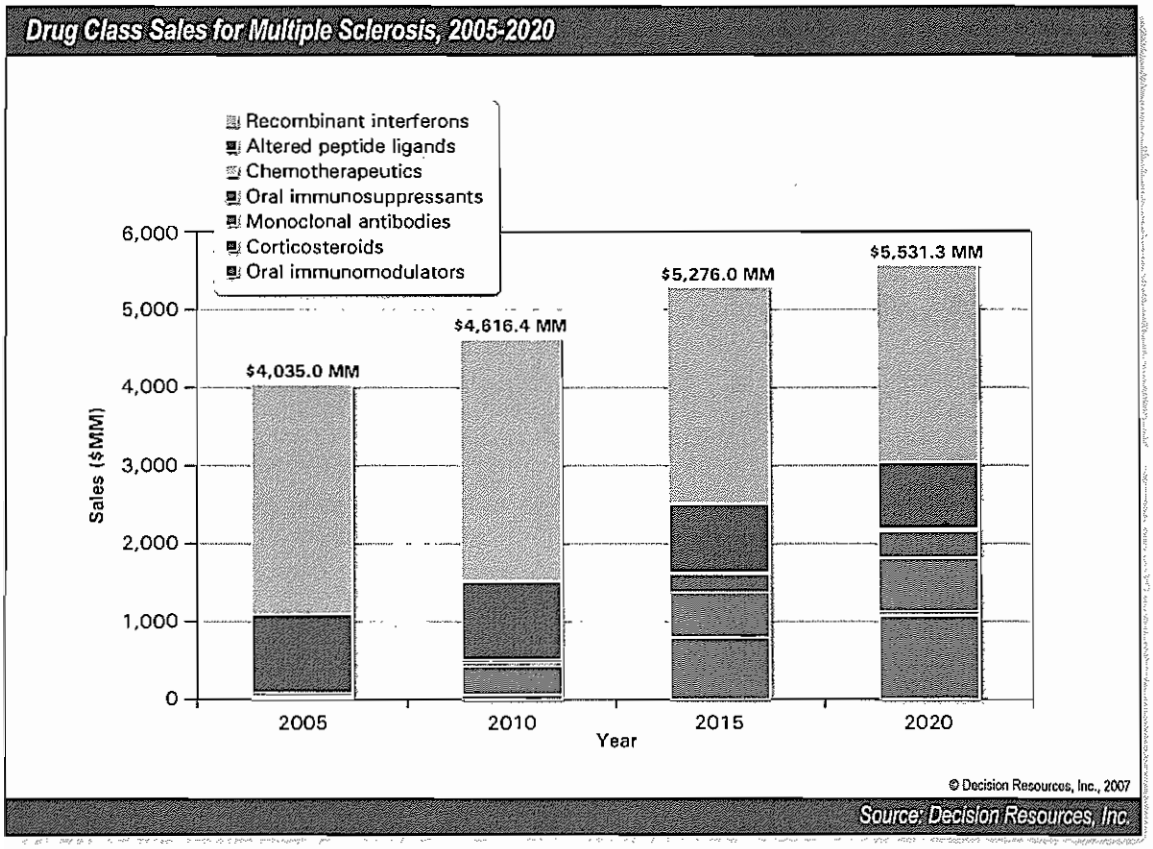
Figure 9-1



only inflammation in MRI studies. Pathological studies have demonstrated that neurodegeneration is independent of inflammation. So, it's as if there are two kinds of different diseases that go together. [Whenever] neurodegeneration starts, [it has] nothing to do with immune suppressants or inmune modulators." Most experts state that because immunomodulatory and neuroprotective agents will likely act on separate aspects of the disease, and neuroprotectants will not affect a patient's immune system, the combination use will not result in more severe side effects than the individual agents alone.

Novel immunosuppressants/immunomodulators, monoclonal antibodies (MAbs), and altered peptide ligands (APLs) will enjoy robust growth rates over our 15-year study period, despite their small patient shares; indeed, they will command high enough price points to garner 32% of 2020 major-market sales. The novel immunosuppressants (Merck Serono's oral cladribine [Mylinax] and Sanofi-Aventis' teriflunomide) and some novel immunomodulators (FTY-720, Biogen Idec's BG-12, and Teva/Active Biotech's laquinimod) all have oral formulations and therefore have a convenience advantage over injectable therapies. These therapies will launch at a premium beginning in 2010 and will start earning modest sales. We forecast that sales of novel immunosuppressants will represent approximately 6% of major-market sales in 2020, while sales of novel immunomodulators

Figure 9-2



will contribute 19% of major-market sales that year. Novel MAbs (i.e., Biogen Idec/PDL BioPharma's daclizumab, marketed as Roche's Zenapax for control of kidney transplant rejection) will capture 2% of the major-market sales in 2020, and novel APLs (i.e., BioMS Medical's MBP-8298) will represent 5% of major-market sales that year. We expect fierce competition among these agents for the limited patient niches consisting of either patients with early-stage MS who do not want to begin the onerous dosing schedule associated with current injectables or patients with aggressive forms of MS that does not respond to current therapies. However, as with natalizumab, we do not believe these novel therapies will garner significant patient share owing to shortcomings in their safety profiles; their modest efficacy will also contribute to their limited patient share. The exception is FTY-720, which will capture 16% of the major-market sales in 2020 because of its superior efficacy over that of other current therapies.

We also expect that erosion from biogeneric IFN-βs will reduce the market share of IFN-β therapies. Biogeneric IFN-βs will first become available in Europe in 2008 and in the United States in 2012, and by 2020, biogenerics will capture approximately 40-65% of the brand share (see Appendix B, "Market Forecast Methodology," for details on generic erosion in all markets). The price of biogenerics will decline throughout the forecast

period; in 2020, we anticipate biogenerics will be 50-70% of the brand price. The average price of biogeneric IFN-βs will not be as low as the price of generic small molecules because of the hurdles that biogeneric manufacturers must overcome to bring their biogenerics to market (see the drug-class-specific sections later in this chapter for more details). However, because reimbursement agencies will likely favor biogenerics over the branded forms, they will capture significant market share and as a result will contribute to the decline in market share of the IFN-βs. (For additional information on the biogenerics market, see the following report: Toward a biogenerics market: the regulatory conundrum. Decision Resources, Inc. *Spectrum, Pharmacoeconomics, Pricing, and Reimbursement.* Issue 19, 2006.)

Three new follow-on products to current therapies will boost sales of IFN-βs despite generic competition. Follow-on products to Betaseron, Rebif, and glatiramer acetate will enter the market during our forecast period. A new formulation of Rebif that is more tolerable than the currently available formulation will launch in the United States and Europe in 2007, and higher-dose forms of Betaseron and glatiramer acetate will launch in the same markets in 2009. By 2020, we expect, the majority of these franchises' market share will be attributed to the follow-on forms. Each drug will be priced at a premium to its respective current formulations and will thus temper the market decline in these franchises.

Of emerging agents, only FTY-720 will experience generic competition during our forecast period, albeit only in the United States beginning in 2019; the drug will receive exclusivity in European markets through 2020, thus preventing the entrance of generics until after the end of our study period. In the United States, the price of generic FTY-720 will be 85% of the brand price. In this report, although FTY-720 will experience generic competition in just one market (United States) for one year of our study period (2020), generics will weaken branded FTY-720's market dominance in that year.

The assumptions underlying our MS market forecast are detailed in Appendix B, "Market Forecast Methodology." The following paragraphs encapsulate factors that are driving sales and/or patient share of agents in the MS market over our study period.

Emerging Therapies

The availability of new MS therapies will contribute significantly to the overall growth of the market; most agents will have only limited patient share but all will be priced at a premium to current therapies and will increase drug-treatment rates. We expect several new compounds to reach the MS market during our forecast period: three oral immunomodulators (FTY-720, BG-12, and laquinimod); two oral immunosuppressants (teriflunomide and oral cladribine); a new MAb (daclizumab); and a new APL (MBP-8298). These therapies will see only moderate uptake because of their modest efficacy and generally unfavorable side-effect profiles, but their high price points will lead to significant sales. The standout emerging therapy is FTY-720. FTY-720 will obtain significant market and patient share because of its superior efficacy, although the potential for serious adverse effects will

somewhat constrain its sales over our forecast period. In 2020, 32% of the MS market will be attributable to therapies still in development in 2005.

Emerging Oral Immunomodulatory Therapies

Novel oral immunosuppressants and immunomodulators will experience the most robust growth rates of all emerging therapies during the middle of our forecast (approximately 59% between 2010 and 2015); their growth rate will slow to 7% through the end of the forecast period.

Sales of immunosuppressants will grow significantly during the latter part of our study period as a result of the launch of oral cladribine and teriflunomide. Oral cladribine will be the first oral therapy to enter the market, and we expect it to launch in the United States and Europe in early 2010. Teriflunomide will enter the U.S. market in 2011 and the European market in 2012. These drugs will have the advantages of oral formulations, but their use will be restricted to aggressive RR-MS as fourth-line therapy because of their potentially poor side-effect profile. They will also be used as fourth-line therapy in SP-MS patients who continue to experience relapses, but they will not be used for PP-MS. Oral cladribine and teriflunomide will capture market share mostly from current disease-modifying therapies. Oral cladribine and teriflunomide will both compete with daclizumab and MBP-8298 in RR-MS and SP-MS patient populations for market and patient share.

Sales of novel immunomodulators will grow substantially during our forecast period because of the launch of three oral immunomodulators: FTY-720, BG-12, and laquinimod. FTY-720, which will launch in the United States in the second half of 2010, in Europe in 2011, and in Japan in 2020, will gain the largest market share in this drug class owing to its oral formulation, superior efficacy, and acceptable safety profile. The drug may be used first-line in patients with early-stage MS and RR-MS who do not want to self-inject and are willing to risk potential opportunistic infections; FTY-720 may also be used fourth-line when early-stage MS or RR-MS patients have become intolerant to current disease-modifying drugs but do not want to use natalizumab because of its potentially fatal side effects. We expect that FTY-720 will also be used fourth-line in SP-MS patients who relapse. FTY-720 will achieve 16% of market share in 2020.

We expect that BG-12 and laquinimod will perform equally well during our forecast period. Both drugs demonstrate modest efficacy and safety profiles, and both will capture market share from current disease-modifying therapies. BG-12 and laquinimod will compete with FTY-720 for patient share in the early-stage MS and RR-MS patient populations; these drugs will be used in patients whose disease has become refractory to current disease-modifying therapies, who cannot tolerate the side effects associated with current injectable therapies, or who do not want to self-inject. We do not anticipate the use of either drug in the CP-MS population. BG-12 and laquinimod will each capture 2% of the market in 2020.

Emerging Injectable Immunomodulatory Therapies

Following its launch in 2009, the novel MAb daclizumab will experience an initial annual growth rate of 20% from 2010 to 2015, slowing to 3% from 2015 to 2020. We expect that the MAb will be used solely as a monotherapy.

Concerns over potential side effects when used in combination with immunomodulators, similar to those seen with natalizumab/Avonex use, will preclude its use in combination. In addition, the drug's modest efficacy will limit its use to aggressive RR-MS and SP-MS. The drug will likely be used fourth-line for patients who are refractory to current disease-modifying therapies and who do not want to use natalizumab because of its potentially fatal side effects. Daclizumab will capture market share from current disease-modifying therapies, achieving nearly $110 million in major-market sales in 2020.

The second injectable immunomodulatory agent to reach the market during our study period, the APL MBP-8298, will have an annual sales growth rate of 14% from 2015 to 2020 following its launch in 2011. MBP-8298 will be used predominantly in the CP-MS population (see the section "Market Segmentation of Emerging Therapies") and will garner nearly $275 million in major-market sales in 2020.

Emerging Follow-On Products to Current Therapies

Reformulations and new dosages of current therapies will contribute modestly to the market success of current IFN-β therapies. A higher-dose form of Betaseron (500 mcg) will launch in 2009. Although it is unclear whether this form is more efficacious than the approved 250 mcg dose, we expect that the 500 mcg form will launch at a premium to the current Betaseron price and will obtain the majority of market share of the Betaseron franchise by 2020; the higher price point of 500 mcg Betaseron will modestly temper the decline of this franchise in all markets. We also expect that a more tolerable reformulation of Rebif (and potentially less-frequent dosing schedule) will launch during our forecast period and will obtain the majority of the Rebif franchise's market share by 2020. The new formulation will launch in 2007 at a premium to the current Rebif price and so will temper the decline in market share that Rebif will experience as a result of competition from other emerging therapies. A higher-dose formulation of glatiramer acetate (40 mg) will also launch in 2009. Because this formulation appears to be as safe and at least as efficacious as the current dose of glatiramer acetate, we expect that its launch will promote increased use in some markets and temper the decline of the glatiramer acetate franchise in others. Although current disease-modifying therapies (and their emerging follow-on products) will lose patient share because of competition from daclizumab, MBP-8298, and the oral immunosuppressants/immunomodulators during our forecast period, the decline in Betaseron's, Rebif's, and glatiramer acetate's market shares will be tempered by the higher price points and improved efficacy and/or tolerability of their respective follow-on products.

Market Segmentation of Emerging Therapies

Most of the current and emerging therapies covered in this report are available for RR-MS. Not surprisingly, most sales of MS therapies over the forecast period will be for the treatment of RR-MS. Sales of drugs to treat RR-MS accounted for more than 80% of the total MS market in 2005, and sales of these drugs will maintain the majority of market share through 2020 (78%). Therapeutic options for CP-MS patients are sorely limited because therapies targeting the immune component of the disease

are largely ineffective in this patient population (they are effective in SP-MS patients with relapses); CP-MS is characterized by neurodegeneration. The considerable unmet need for effective therapies in the CP-MS population represents potential for significant market growth because of these drugs' uptake not only in CP-MS but also in RR-MS patients.

Only one emerging therapy is in development primarily for CP-MS. BioMS Medical is targeting SP-MS patients carrying the *HLA-DR2* or *HLA-DR4* gene (representing 50-75% of the MS patient population, according to experts interviewed) with its drug MBP-8298 (Oksenberg JR, 2005a). The launch of MBP-8298 in 2011 in the United States and Europe will contribute to the growing drug-treatment rate for patients with CP-MS, but it will not dramatically increase sales, which will remain low because of the drug's possible association with hypersensitivity reactions.

Many other emerging therapies are being developed and tested in the CP-MS population, but they are also being tested in RR-MS, and it is likely that these agents will be used predominantly for RR-MS. Daclizumab, oral cladribine, laquinimod, and teriflunomide are each being tested in RR-MS and SP-MS populations. We expect that oral cladribine, teriflunomide, and FTY-720 will be used primarily in SP-MS patients who continue to relapse and, as a result, will garner only limited market share in this patient population because of the small prevalence of this population. Daclizumab will be used for SP-MS and may experience limited off-label use in PP-MS. However, additional therapeutic options for SP-MS will remain limited. Biogen Idec and Genentech are testing the MAb rituximab in PP-MS, affording these patients a therapeutic option; however, in the absence of efficacy and safety data, we are unable to forecast a launch for this agent. Overall, we expect to see incremental market growth of 3-5% in sales of drugs to treat CP-MS during our forecast period.

Oral vs. Parenteral Formulations

Physicians interviewed note that efficacy, more than formulation, motivates patients' drug choices. Given the modest efficacy data thus far available for cladribine, teriflunomide, BG-12, and laquinimod on progression of disability, we anticipate that uptake of these drugs will be moderate, despite their oral formulations. Experts interviewed stress the need for oral therapies but are pessimistic about oral therapies achieving significant efficacy. One expert notes, "Efficacy is always the most important of all criteria in deciding which way you want to go. Just as you would give injectable steroids for relapses to MS patients over oral steroids, if injectable treatment was superior to an oral drug, we'll use the injectable, and patients will accept that."

The poor side-effect profile of oral immunosuppressants and immunomodulators will further limit their patient share. As one expert interviewed points out, "It's not worth increasing the risk to patients just to get an oral therapy. I think there has to be a balance between the benefits and the risks."

Because an agent with an oral formulation would theoretically enjoy robust market uptake in a market of injectables, drug developers are aggressively competing to bring the first oral MS therapy to market. Experts interviewed

by Decision Resources state that although oral therapies are needed, efficacy is the main driver of the MS market, and emerging therapies must demonstrate sufficient efficacy before they will be widely used as MS therapies. However, as one expert notes, "If you are talking about equal efficacy, then clearly, oral treatment will have an advantage."

Frequency of Administration and Compliance

Frequency of administration of a therapy is one of the key drivers of uptake in the MS market. For instance, Avonex is often the preferred IFN-β in large part because of its low frequency of administration compared with Betaseron and Rebif. However, infrequent administration does not necessarily make a drug more attractive to patients. Most experts interviewed state that efficacy is the primary concern for patients and that tolerability and safety are secondary, but all three take precedence over convenience. Indeed, glatiramer acetate, which is administered as a daily subcutaneous injection, obtained the second-largest market share behind Avonex in 2005 (25% compared with Avonex's 34% in the United States and Europe combined), and we expect Avonex use to decline during our forecast period as oral therapies, many of which also require daily dosing, enter the market. One emerging therapy in particular, oral cladribine, appears to have a significant advantage in administration because of its twice-yearly dosing regimen over the course of four to five days, which will likely improve compliance.

In addition to a drug's efficacy, many experts state that the safety profile of emerging therapies is critical as well. As one expert explains, "Safety is going to be super important--more so than anybody would have even thought of before Tysabri. I think that's woken us up." Because the MS market has become sensitized to the risks of severe side effects, many experts are wary of emerging therapies because of the lack of safety data. According to one expert, "If it's an oral agent with equal efficacy or even lesser efficacy than the current treatments, it's going to have a place in the market, if it's safe. I still might lean toward the injection therapies up front, because we know they're safe, and if the patient does well, then keep them on that therapy. As time goes on, we'll learn more about the safety of the other agents."

Many neurologists note that compliance issues would be significantly improved with a daily oral therapy despite the high-frequency dosing. According to one expert, "I know the data show that the disease-modifying drugs we have don't work orally, so whether that can be overcome, whether there can be drugs that will work through an oral delivery system I don't know, but I think it would be a very big benefit to patients and compliance generally." Experts interviewed note that the emerging therapies offer additional therapeutic options to patients, which will increase overall compliance as well as persistence. As one Italian neurologist explains, "The more alternatives we have, including oral treatments, will further increase compliance, not only in terms of the absolute figure but also in terms of continuing a therapy for longer periods of time without changing from one to another."

Drug-Class-Specific Trends

Recombinant Interferons

Branded Interferons

Beeause none of the therapies slated to launeh during our study period will prove safer than currently available therapies, the IFN-βs will remain the leading drug class in the MS market, capturing 45% of the total dollar market in 2020 (see Figure 9-1). Competition from biogeneric forms of IFN-βs and from emerging agents will reduce the IFN-βs' dominance in the MS market, but follow-on products to Betaseron, Rebif, and glatiramer acetate, whieh we expeet to launch at a premium during our forecast period, will temper the decline in market share of branded IFN-βs through 2020.

Avonex is the market leader among the IFN-βs; in 2005, its sales represented just over one-third of the total MS dollar market. Its sales will decline during our forecast period, from approximately $1.36 billion in 2005 to $780 million in 2020. The increase in the drug-treated population throughout our study period will not be sufficient to offset a decline in patient share (from 35% in 2005 to 20% in 2020) and, thus, in sales. This will be the case particularly in early-stage MS patients, a group in which Avonex has shown therapeutic efficacy in delaying the occurrence of a second relapse (see Chapter 4, "Current Therapies and Treatment Trends," for details on the results for Avonex in the CHAMPS trial). We expect that the drug will lose patient share to Rebif owing to data from the EVIDENCE trial showing Rebif's superior efficacy; in addition, the reformulation of Rebif, which has improved safety and is being investigated at a dosing frequency similar to that of Avonex (once weekly), will steal patient share from Avonex upon its launch in the United States and Europe in 2007. Avonex will also lose patient share to emerging therapies such as FTY-720 (in those patients willing to accept the risk of opportunistic infections), BG-12, and laquinimod, which will provide alternate therapeutic options for early-stage MS and RR-MS.

Avonex will retain significant patient share through 2020 (20%) because of its convenience (once-weekly administration, compared with three times weekly for Rebif and every other day for Betaseron), but in 2020, the drug will no longer be the patient-share leader; increased use of Rebif during the forecast period will result in both drugs capturing 20% patient share in 2020.

The 2002 U.S. launch of Rebif for the treatment of RR-MS has not hurt Avonex's market share as much as had been expected: Rebif captured only a 21% share of total U.S. MS sales in 2005. However, increased sales of Rebif (and glatiramer acetate) have in large part driven the increase in the U.S. and European markets since 2003, growing at annual rates of 17% and 14%, respectively. Rebif's increase in patient share has by far outpaced that of the other IFN-βs in the United States over the past two years. Similarly, Rebif's uptake has been particularly strong in France, Italy, Spain, and the United Kingdom over the past two years; experts interviewed see Rebif as more efficacious than Avonex, based on data from the EVIDENCE trial, which suggests that Rebif is superior to Avonex for the treatment of RR-MS (see Chapter 4, "Current Therapies and Treatment Trends"). Emphasizing that efficacy is the primary consideration in therapy choice, one neurologist

states, "I think there's enough information to indicate that there is greater efficacy with the higher-dose interferons." In addition, Rebif's July 2006 approval for use in early-stage MS will continue to fuel growth because MS is being diagnosed earlier and physicians are increasingly prescribing therapies for these patients.

The perception of Rebif as a more-effective IFN-β therapy will fuel a modest increase in patient share, at the expense of Betaseron and Avonex, from 15% of drug-treated patients in the United States in 2005 to 17% in 2020. It will also fuel the drug's 6.2% compound annual sales growth rate in the United States over the first third of the forecast period (2005-2010). We expect the growth in U.S. market share to slow after 2010 as Rebif loses patient share in part to natalizumab, FTY-720, and other emerging therapies. Rebif's sales growth in Europe will also be the highest over 2005-2010 (4% compound annual growth), owing in large part to the dramatic growth of the agent in the United Kingdom (20% compound annual sales growth rate over 2005-2010), before slowing after 2010. Although Rebif's patient share in RR-MS will decline starting in 2015 as a result of competition from emerging therapies, its market-share decline will be tempered by increased patient share in the SP-MS population through 2020.

Phase I studies of Rebif were suspended in Japan, and we do not expect the drug to launch in this country because its development is not commercially attractive for Merck Serono. First, the prevalence of MS in Japan is small compared with prevalence in the United States and Europe—1.6% of total MS prevalence in the major markets in 2005. An additional drawback are the pricing restrictions imposed on drugs that are not first to market in Japan, a restriction that would affect Rebif, which is third to market. In addition, the Japanese regulatory agency, the Ministry of Health, Labor, and Welfare (MHLW), will likely approve Rebif only if Merck Serono presents clinical trial data run on Japanese MS patients. The MHLW is still cautious about the influence of ethnic factors (both genetic and cultural) on the testing of drugs in Japan, a problem that is particularly pronounced in the case of MS owing to its low prevalence in that country. Although the MHLW passed legislation in 1998 to promote use of clinical data obtained in countries other than Japan (International Conference on Harmonization guideline E5—Ethnic Factors in the Acceptability of Foreign Clinical Data), few new drug applications that used partial data from non-Japanese trials have been approved—18 between 1998 and 2003. (For more information, see the following report: International trends in pharmaceutical regulatory affairs. Decision Resources, Inc. *Spectrum, Pharmaceutical Industry Dynamics.* Issue 18, 2003.) Supporting this genetic influence is the fact that, unlike in the United States and Europe, the predominant form of MS in Japan affects the optic nerve (neuromyelitis optica), and Japanese neurologists interviewed mention that IFN-β treatment is not efficacious in this type of MS. Experts also note, however, that the type of MS in Japan has been moving toward a "Western type of MS" for the past 30 years, and they warn that if the Western type of MS increases rapidly, the lack of treatment choices in Japan will become an issue. Because of regulatory and pricing restrictions and the small Japanese MS population and market size, Merck Serono will not be guaranteed a return on investment in costly Japan-based clinical trials.

During the forecast period, we expect major-market sales of Betaseron to decline from $740 million in 2005 to $490 million in 2020. Betaseron's sales have been and will continue to be affected by competition from other disease-modifying therapies, particularly Avonex for patients with early-stage MS who are reluctant to undertake Betaseron's onerous dosing schedule but also Rebif for early-stage MS and RR-MS. In addition, experts are interested in the reformulation of Rebif and indicate that they are likely to continue Rebif use. As one expert states, "I don't use as much Betaseron now that Rebif is available just because of a somewhat lower neutralizing antibody rate with beta 1a [Rebif] and that may be further improved with the new formulation that's going to come out." This decline in sales will be most apparent in Japan, where Betaseron is no longer the only disease-modifying drug on the market following the launch of Avonex in November 2006. Yet, Betaseron will retain some patient share owing to its use in SP-MS patients, for which it is the only IFN-β therapy approved in the United States and Europe, and to data that suggest that high-dose, frequently administered IFN-β therapies are more effective than low-dose, less frequently administered IFN-β therapies, such as Avonex (Deisenhammer F, 2000; Goodin DS, 2002).

Efforts to expand labeling for Betaseron, Avonex, and Rebif to include treatment of early-stage MS will be modestly lucrative. Avonex and Rebif have been approved for the treatment of early-stage MS in Europe, and in October 2006, Bayer Schering Pharma/Berlex received approval for Betaseron to treat early-stage MS in the United States. The majority of experts interviewed state that they prescribe disease-modifying therapies for early-stage MS patients because, as one physician states, "patients tend to do better the earlier that treatment is started." However, they note that not all patients diagnosed with early-stage MS receive disease-modifying agents upon diagnosis, either because the physicians are unconvinced about treatment benefits at that stage (according to experts interviewed, 20-30% of early-stage MS patients will not have another relapse within the next five years) or because regulatory agencies and third-party payers fail to cover the costs of these agents in early-stage MS patients.

Currently, Betaseron is approved to treat SP-MS in Europe and SP-MS with relapses in the United States; Avonex is approved to treat SP-MS with relapses in Europe. Although we anticipate that IFN-β therapies will eventually be approved for SP-MS in all seven major pharmaceutical markets, we forecast that these drugs will achieve approval only for the treatment of SP-MS patients who continue to relapse (for a detailed discussion, see Chapter 4, "Current Therapies and Treatment Trends"), a much smaller and less profitable patient population than the entire SP-MS population. Physicians estimate that this subgroup represents 40% of SP-MS patients, equal to 10-12% of total diagnosed MS cases. Limited off-label use of IFN-β therapies in PP-MS may occur, given the lack of therapeutic options for this patient population. However, because PP-MS does not have an immune component, IFN-βs will not likely be efficacious in this population, so patient share for these drugs in CP-MS will continue to be very limited.

Biogeneric Interferons

New legislation to introduce generic biologics is being considered in the United States and is already in place in Europe, and we expect modest generic erosion of IFN-β therapies by the end of our forecast period. The development and regulatory hurdles that generic biologics must overcome remain daunting, but we expect generics manufacturers to launch biogeneric versions of IFN-βs at sizeable discounts in order to steal significant patient share from the branded forms.

With sales of IFN-βs totaling nearly $3 billion in the seven markets under study in 2005 (73% market share), combined with the class's continued dominance through 2020 (45% market share), MS is an attractive market for biogeneric manufacturers. Competition is fierce among the three IFN-βs, and IFN-βs will still be highly utilized over our forecast period, maintaining 45% of market share in 2020. Natalizumab's recent loss in projected market share has allowed IFN-βs to retain market share, but as emerging agents are increasingly used, the market share of IFN-βs will decline. We expect FTY-720 to provide the strongest competition of all emerging agents because of its superior efficacy and acceptable safety profile, but other emerging agents will also capture market share from IFN-βs in niche patient populations in which IFN-βs are typically prescribed. We expect that glatiramer acetate's uptake in the United States and Europe will slow over our forecast period, so the drug will steal relatively little patient share from the IFN-βs.

Bayer Schering Pharma, Merck Serono, and Teva's follow-on products to Betaseron, Rebif, and glatiramer acetate, respectively, which we expect to garner the majority of patient share of those respective branded agents by 2020, will provide additional competition for biogeneric forms of current IFN-β therapies. However, third-party payers, eager to curb the expenses associated with branded versions of IFN-βs, will likely encourage the use of biogeneric versions in all the markets under study.

Only three companies appear to be developing biogeneric versions of IFN-βs--BioPartners/Rentschler, GeneMedix, and Prolong Pharma--ensuring little competition among these drugs and limiting price erosion. All three companies have the infrastructure necessary to develop biologics. BioPartners, which entered into an agreement with Rentschler in 2002 to develop biogeneric IFN-β, is based in Switzerland and is developing biogeneric versions of erythropoietin, colony-stimulating factors, and IFN-β; the company also received approval in 2006 in Europe for its recombinant human growth hormone (Valtropin). BioPartners' biogeneric IFN-β appears to be furthest in development (Phase III), and the company expect to file in Europe in the first half of 2007, although no submission has occurred as of February 2007. GeneMedix, based in the United Kingdom, focuses on the development of biogenerics and is developing generic versions of several biologics, including erythropoietin, human granulocyte colony-stimulating factor, insulin, recombinant human growth hormone, and IFN-α. GeneMedix is considering inlicensing the generic compound from a partner. Prolong Pharma, based in the United States, is developing erythropoietin, granulocyte colony-stimulating factor, and IFN-α. Bioceuticals Arzneimittel, a company closely associated with Stada Biogenerics (a subsidiary of Stada

Arzneimittel), was developing a biogeneric IFN-β, but development of the compound was discontinued in November 2006; the company chose to focus its resources on developing erythropoietin and granulocyte colony-stimulating factor (filgrastim).

We expect that biogeneric forms of IFN-βs will be priced markedly lower than the price of branded forms; in 2020, biogeneric versions of IFN-βs will be priced at 50-55% of the brand price in the United States and 60-70% of the respective brand prices in each European market. These agents will be priced at a discount to branded forms despite the cost and technical hurdles that manufacturers will have to overcome to bring the drugs to market; the IFN-β protein is challenging to manufacture, and several issues associated with the protein's immunogenicity (e.g., the development of neutralizing antibodies) have arisen with branded versions of the drug. In addition, drug developers will likely have to run complete Phase III trials lasting at least two years and using clinical end points (because no surrogate markers for the disease are available and because MRI end points correlate poorly with clinical end points such as disability progression) to demonstrate the drug's safety and bioequivalence to branded IFN-βs. Regulatory agencies will also likely require manufacturers to run postmarketing surveillance programs, particularly in a market sensitized to safety issues because of natalizumab's withdrawal. However, when biogenerics become available, their use will likely be favored by reimbursement agencies.

Overall, neurologists interviewed are willing to prescribe biogeneric versions of IFN-βs, although they note the decision will be dictated largely by third-party payers. Some physicians, however, are skeptical about the efficacy of a biogeneric version and stress the importance of clinical trials in determining the efficacy of biogenerics. One expert states, "I would be happy to prescribe a biogeneric, but I would care about studies. If it would be approved upon randomized controlled trials and if the efficacy is the same as the branded one, I would prescribe it."

The European Medicines Agency (EMEA) was slated to draw up guidelines on the manufacture of biogeneric interferons in 2006, although no information was available as of February 2007; the agency has already issued product-specific guidelines covering other major classes of biosimilars. In February 2007, the Access to Life-Saving Medicine Act was reintroduced in Congress (similar legislation was introduced in a previous session of Congress in late September 2006), but no action was taken on it before Congress adjourned. This legislation would allow abbreviated biogeneric applications based on BLA-registered "reference" products. The act provides the FDA with discretion to examine each applicant on a case-by-case basis and allows the agency to require clinical studies--but only as needed--to establish comparability between the originator product and the biogeneric. It is unclear how much litigation will surround the launch of biogenerics, but given the historical wrangling surrounding orphan-drug status challenges among manufacturers of branded IFN-βs, we expect the biogeneric manufacturers to encounter some resistance from brand manufacturers. We anticipate that generic versions of IFN-βs will become available in 2008 in Europe and beginning in 2012 in the United States.

Altered Peptide Ligands

One of the major MS market drivers between 2003 and 2005 was the uptake of glatiramer acetate in the United States and Europe; the drug's patient share expanded from 21% in 2003 to 30% in 2005 in these markets because of its launch in European markets (e.g., September 2003 in France). We expect no market growth of glatiramer acetate in the United States over the next five years and slow-to-modest growth in Europe through 2010. Although glatiramer acetate launched later than the IFN-βs in the European markets, it has performed remarkably well, generating higher seven-market sales than Betascron and Rebif in 2005. Neurologists interviewed in the United States and Europe state that glatiramer acetate's relatively benign side-effect profile has encouraged its use as a first-line therapy, especially for patients intolerant of or refractory to IFN-β therapy, and for patients suffering from mild MS. The absence of flulike side effects largely accounts for the drug's commercial success.

Sales of glatiramer acetate will decline between 2010 and 2020 as a result of generic erosion and declining patient share in the United States in favor of emerging therapies, particularly FTY-720. In 2015, Rebif sales will surpass glatiramer acetate sales; in 2020, glatiramer acetate will capture approximately $424 million in U.S. sales, behind that of both Avonex and Rebif.

In Europe, glatiramer acetate sales will increase slightly through 2010, from $199 million in 2005 to $229 million in 2010, because of the drug's use in early-stage MS as well as the launch of the drug's higher-dose formulation. The high price point of the higher-dose formulation, combined with increased use over the original dose, will contribute to these sales. However, by 2020, competition from emerging agents beginning in 2010 and generics in 2015 will reduce glatiramer acetate's market share to 8% in Europe in that year, with $166 million in sales. We do not expect the drug to launch in Japan owing to the country's small number of MS patients.

We expect MBP-8298 to launch in 2011 in the United States and Europe. The drug appears to have efficacy only in a subgroup of patients who carry the *HLA-DR2* or *HLA-DR4* gene (an estimated 50-75% of diagnosed MS patients). We expect that MBP-8298 will obtain the majority of its patient share in CP-MS, particularly SP-MS patients; BioMS Medical is investigating MBP-8298 in RR-MS as well, but we expect that the drug will obtain only limited patient share in this population. Indeed, in both RR-MS patients and SP-MS patients who continue to relapse, the drug will be competing with the disease-modifying drugs (IFN-βs and glatiramer acetate) for patient share. In these patients, we anticipate that MBP-8298 will be used as a second- or third-line therapy once patients have failed disease-modifying drugs. However, we expect that the drug will enjoy relatively little competition in SP-MS patients who do not relapse because alternative therapies for this patient population (mitoxantrone and, to some extent, natalizumab) will have worse side-effect profiles. MBP-8298 may also obtain small patient shares in PP-MS patients, based on data from a small-scale Phase II trial showing that MBP-8298 delayed disease progression in progressive MS patients by five years compared with placebo (Warren KG,

2006). Because MBP-8298 will garner only modest patient share, the drug will not generate sufficient sales to offset the decline in sales of APLs. In 2020, MBP-8298 will earn $274 million in major-market sales.

Chemotherapeutics

The contribution of chemotherapeutic agents—e.g., mitoxantrone (Merck Serono/Amgen's Novantrone), methotrexate (Wyeth's Rheumatrex, generics), cyclophosphamide (Bristol-Myers Squibb's Cytoxan, generics)—to overall MS market value will be modest. Mitoxantrone is the only drug in this class that is approved for MS in the United States; methotrexate and cyclophosphamide are prescribed off-label. Major-market sales in this drug class will decline over the course of the study period, from $46 million in 2005 to $13 million in 2020. Their toxicity, the paucity of the data supporting their efficacy, and physicians' bias against broad-spectrum immunosuppressants as first-line therapy will relegate these drugs to fourth-line or adjunct treatment for RR-MS patients who do not respond to treatment. We expect the already-limited patient shares of these agents in RR-MS to decline by 2020 as a result of the increased number of disease-modifying therapeutic options that will launch over the forecast period. Even if patients fail current disease-modifying therapies, they will be treated with one or more emerging agents prior to beginning treatment with a chemotherapeutic agent.

Chemotherapeutic agents are used most extensively to treat CP-MS patients, particularly the PP-MS population, which currently has no efficacious therapeutic options. The launch of MBP-8298 in 2011 will take limited market share from the chemotherapeutics, namely mitoxantrone in the CP-MS market, particularly in the CP-MS subgroup of SP-MS patients who do not relapse. However, MBP-8298 will not have a significant impact on sales of mitoxantrone in the 25-50% of SP-MS patients who do not carry the *HLA-DR2* or *HLA-DR4* gene. Daclizumab and mycophenolate mofetil (MMF, Roche/Aspreva/Chugai's CellCept) will also steal market share from mitoxantrone in PP-MS patients.

Oral Immunosuppressants

Azathioprine (GlaxoSmithKline's Imuran, generics) accounts for a small portion of major-market sales; azathioprine is approved for renal transplantation and rheumatoid arthritis and is used off-label for MS. It is typically administered to a small percentage of RR-MS and CP-MS patients who have failed IFN-β therapy, sometimes in combination with IFN-β or glatiramer acetate therapies but often as a monotherapy. Despite the drug's oral formulation, it is little used because of its side effects, which include an increased risk of cancer and opportunistic infections, reduced white blood cell count (leukopenia), and the need for blood monitoring. We expect major-market sales of azatbioprine to decline over the course of our study period from $5.7 million in 2005 to $3.4 million in 2020.

MMF is approved for transplant rejection and is sometimes used off-label for MS, primarily in the United States and France. In 2005, the drug earned $4.9 million in sales in MS. MMF captures the largest patient share in CP-MS patients in France (10%), specifically in the PP-MS patient population,

although limited use has been reported in the treatment of aggressive RR-MS as well. In the United States, MMF is restricted to a small percentage of PP-MS patients who have no other therapeutic options. We expect that sales of MMF will increase to $5.1 million in 2010 but then decline to $3.2 million in 2020 as a result of competition from emerging therapies that are safer and more efficacious.

Sales of immunosuppressants as a class will increase significantly during our study period—from $10.6 million in 2005 to $343 million in 2020—fueled chiefly by the launches of oral cladribine and teriflunomide. We expect oral cladribine will launch in the United States and Europe in early 2010. As the first oral therapy to market, we expect cladribine to gain modest market share by the end of our forecast (3.7% in 2020), with $203 million in sales; its uptake will be limited, however, because the drug's convenient oral formulation will not outweigh its moderate efficacy and potential safety risks. Teriflunomide will launch in 2011 in the United States and 2012 in Europe; as the second oral immunosuppressant to market, it will not experience as rapid an uptake as oral cladribine, garnering sales of $133 million in 2020. In clinical trials thus far, teriflunomide's safety profile appears to be worse than that of oral cladribine, a fact that will constrain the drug's uptake. Also, the launch of the more-efficacious FTY-720 in 2010 will provide additional competition that will limit teriflunomide's uptake. Both oral cladribine and teriflunomide will be used as third-line therapy to natalizumab and IFN-β therapy for aggressive RR-MS and will compete with daclizumab, MBP-8298, and FTY-720 for patient share in this population. Oral cladribine and teriflunomide will be used in CP-MS patients; oral cladribine will likely be used second- or third-line to the IFN-βs and FTY-720 in SP-MS patients with relapses, while teriflunomide will be used third-line. Oral cladribine may also be used in a small percentage of SP-MS patients who no longer experience relapses. These uses will claim only a very small patient share because of the drugs' safety profile, but these agents' high prices and convenient oral formulation will ensure a modest market share: 6% in 2020 (see Figure 9-1).

Monoclonal Antibodies

The only novel MAb to launch for MS during our forecast period is daclizumab, which we expect to launch in 2009 in the United States and 2010 in Europe. As the second MAb to market behind natalizumab, daclizumab will have difficulty gaining market share because, we believe, it will not offer any greater benefits than natalizumab in terms of efficacy or side effects. The drug will obtain only a small patient share in RR-MS (2% in the United States from 2010 to 2020 and 1-2% in Europe from 2015 to 2020) because its use will likely be restricted to fourth-line therapy after the IFN-βs and natalizumab for aggressive RR-MS; the drug will obtain slightly more patient share in CP-MS (2-5% in 2020) because of its use in SP-MS patients who relapse. In all patient populations, daclizumab will compete with FTY-720, oral cladribine, teriflunomide, and MBP-8298 for patient and market share. Daclizumab will have nearly $110 million in major-market sales in 2020.

Oral Immunomodulators

Sales of immunomodulators for MS will reach $1.1 billion in 2020, 19% of major-market sales, owing to the launch of FTY-720, BG-12, and laquinimod. We expect FTY-720 to launch in the second half of 2010 in the United States, in 2011 in Europe, and in 2020 in Japan. Although this drug will not be the first oral therapy to market, its demonstrated efficacy (including efficacy superior to that of current IFN-β therapies on clinical end points) and acceptable safety profile will result in an annual growth rate of 64% over 2010-2015 as the drug rapidly gains patient share in the treatment of aggressive RR-MS and of patients with RR-MS who do not respond adequately to IFN-βs and glatiramer acetate; the annual growth rate will slow to 5% over 2015-2020 because of the emergence of additional therapies targeted at the same niche populations. Of all emerging therapies, we expect FTY-720 to have the largest impact on the market, accruing nearly $870 million in sales, or a 16% market share, in 2020.

In 2020, FTY-720's patient share will be higher than that of other emerging agents, Betaseron, and, in some markets (i.e., United States and Europe), glatiramer acetate. FTY-720 will be used primarily third-line after the IFN-βs and glatiramer acetate in RR-MS and early-stage MS. The drug will be used third- or fourth-line to treat patients with aggressive RR-MS whose disease is refractory to or who cannot tolerate natalizumab and the IFN-βs; it will compete with BG-12 and laquinimod for patient share in early-stage MS patients who are willing to accept the risk of opportunistic infections and with daclizumab, MBP-8298, oral cladribine and teriflunomide in the treatment of aggressive RR-MS. In CP-MS, use of FTY-720 will be limited to SP-MS with relapses, where it will garner 3-5% of major-market patient share in 2020. In Japan, FTY-720 will capture only limited patient share in both RR-MS and CP-MS owing to the small MS population in Japan, the drug's late launch in this market during our forecast period, and generally slow uptake of new therapies in this market.

FTY-720 will experience generic competition beginning in 2019 in the United States, but it will continue to hold market exclusivity in Europe through the end of the forecast period. Generic FTY-720 will be priced at a modest discount to the brand (85%), but this discount will be sufficient to negatively affect the market share of the branded form, particularly because use of FTY-720 will be greatest in the United States, so the availability of a generic will hurt the drug's sales in its largest market.

The oral immunomodulator BG-12 will launch in Europe in 2011 and in the United States in 2012; laquinimod will launch in both the U.S. and European markets in 2012. Because neither drug will be the first-in-class to reach market and because of their modest efficacy and safety profiles, we expect that both agents will be used only by a limited number of early-stage MS patients who refuse to inject and who are unwilling to risk the potential for opportunistic infections associated with FTY-720. In 2020, BG-12 and laquinimod will each garner nearly $100 million in sales.

Region-Specific Trends

Estimated at nearly $2.7 billion in 2005, U.S. sales of MS therapies accounted for 67% of major-market sales. The United States accounts for the greatest share of the MS market because U.S. physicians are more likely than their European and Japanese counterparts to prescribe high-priced, disease-modifying agents.

The United States will remain the largest market for MS drugs throughout the 2005-2020 study period and will experience a small annual growth (approximately 1.7%) as diagnosis rates increase slightly, more physicians begin to treat underserved patient populations (e.g., early-stage MS, SP-MS with relapses, PP-MS), and new therapies become available. Growth will be constrained to some extent because the U.S. market is already highly saturated; the estimated drug-treatment rate is 75%.

Growth in the European markets will be slightly more robust--3%. Although Europe's drug-treated MS population in 2005 was about the same size as that of the United States, the lower cost of drugs in Europe, budgetary restrictions limiting the use of disease-modifying drugs in some European countries (particularly the United Kingdom), and the slow uptake of the disease-modifying agents resulted in significantly lower market share (in dollar terms) compared with the United States. In 2005, sales of drugs to treat MS in the five European countries under study totaled nearly $1.3 billion—32% of major-market sales.

We anticipate moderate annual growth (3.8%) in the European MS market from 2005 to 2015 as disease-modifying drugs gain acceptance and greater use; the acceptance of emerging agents will also promote market growth. Sales growth will slow over 2015 to 2020 to 1.5% as novel therapies saturate currently underserved patient populations. Sales growth will be most dramatic in the United Kingdom, where governmental restrictions on the use of disease-modifying drugs are being relaxed; as a result, by 2020, the drug-treated RR-MS population will have increased by 30% and the CP-MS population by 18%. Historically, the United Kingdom has been the only country in Europe to tightly restrict the use of disease-modifying drugs, but a risk-sharing scheme, whereby pharmaceutical companies reimburse the government for disease-modifying therapy if patients do not improve during drug treatment, is slowly making MS drugs more accessible to patients. However, experts interviewed by Decision Resources suggest that many patients still do not have access to these drugs, and sales do not reflect a robust uptake of these drugs despite the risk-sharing scheme.

The Japanese MS market is very small compared with the U.S. and European markets. In 2005, sales of drugs for MS in Japan totaled $36.4 million—less than 1% of major-market sales. Japan's MS market is minute owing to the small number of prevalent MS cases, a limited repertoire of drug therapies (only Betaseron and Avonex are approved in Japan), and consequently, a smaller drug-treated population (the Japanese drug-treated population is 3% of the U.S. drug-treated population). Because of the small market size, we expect some drug companies to abandon launch projects in Japan; for instance, we do not expect the launch of Rebif or glatiramer acetate in the

Japanese market because its small size makes development of these therapies not worthwhile. The only emerging agent we expect to launch in Japan is FTY-720, which will launch in Japan in 2020, because the parent company, Mitsubishi Pharma, is based in Japan and will likely pursue approval for the drug in its home market. Currently, FTY-720 is in Phase II development in Japan only for renal transplantation.

We expect sales of MS therapies in Japan to increase at an annual rate of 1.9% over the 2005-2020 study period. This growth comes from the launch of three agents in this market, as well as increased drug-treatment rates over the second half of the study period. Avonex, the second disease-modifying therapy to launch in Japan, was introduced in 2006; the drug will enjoy moderately rapid uptake, claiming 37% patient share in RR-MS and 15% in CP-MS in 2020 owing to its more-convenient dosing frequency compared with Betaseron. Additional growth will result from modest uptake of natalizumab after its launch in 2012, offsetting the declining use of some chemotherapeutic agents. FTY-720 will launch in 2020 and will obtain only limited patient share during its initial year on the market (1%). Unlike the U.S. and European markets, the Japanese market will not see the launch of many other emerging agents for MS to fuel market growth.

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MULTIPLE SCLEROSIS 2005-2020

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Appendix A

Bibliography

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.5401.2615 ♦ Fax +81.3.5401.2617

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Appendix B

Market Forecast Methodology

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.54D1.2615 ♦ Fax +81.3.54D1.2617

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Appendix B. Market Forecast Methodology

General Sources of Data

Estimates for the 2005 market for multiple sclerosis (MS) in the seven major pharmaceutical markets we cover (United States, France, Germany, Italy, Spain, United Kingdom, and Japan) are based on a variety of sources, including physician interviews, sales audits, prescribing surveys, published articles, company reports, press releases, and general news media. Market totals for patient share that exceed 100% occur when patients are prescribed more than one drug. The estimated compliant days of therapy with each drug are determined from prescribing surveys, physicians' comments, and estimated compliance rates.

Diagnosed and Drug-Treated Populations

Percentage Diagnosed

We used the following sources to estimate the percentage of prevalent cases that are diagnosed:

- *Published studies.* (Baum HM, 1981; Granieri E, 2000; Lublin FD, 2002; McDonald WI, 2001; Nicoletti A, 2001; Pina MA, 1998; Polman CH, 2005; Poser S, 1995).
- *Opinions of thought leaders.* We conducted in-depth interviews with 34 neurologists throughout the major markets who shared with us their insights into diagnosis rates, patterns, and medical practices.
- *Estimates from the American Multiple Sclerosis Association.*

Our methodology for determining diagnosed prevalence of MS is described in the "Methodology Overview" section of Chapter 3, "Epidemiology and Disease Populations." As reported in that section, we relied on studies that provided diagnosed prevalence for our epidemiology estimates. To estimate the total number of prevalent cases in each country in the first year of our forecast, we assume that 81% of all relapsing-remitting (RR-MS) cases and 96% of chronic-progressive (CP-MS) cases were diagnosed. We then assumed that a weighted average of 86% of all prevalent MS cases in the first year of our forecast period were diagnosed, an estimate that is supported by data from the U.S. National Multiple Sclerosis Survey, which found that approximately 14% of the prevalent MS population is unaware that they have the disease (Baum HM, 1981). We further assumed that the percentage of CP-MS patients who are diagnosed is higher than the percentage of RR-MS patients who are diagnosed because the vast majority of CP-MS patients have secondary progressive MS (SP-MS) that has advanced from RR-MS and, given the duration of their disease, have likely been recognized. The symptoms of SP-MS are more easily recognized, and most SP-MS sufferers were likely diagnosed at the relapsing-remitting stage. The remaining CP-MS patients have primary progressive MS (PP-MS), which is characterized by disease progression from onset, unlike RR-MS. Because of the severity of PP-MS, most patients are likely to be recognized early in the disease process.

We forecast a modest increase in the percentage of patients diagnosed over the course of our study period because of increased availability of magnetic resonance imaging (MRI) equipment and neurologists in the seven markets under study. The publication and expanded use of the McDonald diagnostic criteria (McDonald WI, 2001; Polman CH, 2005) are reducing the lag time between disease onset and a definitive diagnosis of MS (Granieri E, 2000; Nicoletti A, 2001; Pina MA, 1998; Poser S, 1995). However, it is not yet clear whether or to what extent the expanded use of the McDonald criteria will increase the number of patients diagnosed with MS (Lublin FD, 2002).

Percentage Drug-Treated

We used the following sources to estimate the percentage of diagnosed prevalent cases that are drug-treated:

- *Opinions of thought leaders.* We conducted in-depth interviews with 34 neurologists throughout the major markets who shared with us their insights into diagnosis rates, patterns, and medical practices.

The percentage of MS patients who receive drug treatment varies considerably in the markets under study because of varying medical practice and regulatory environments. Our estimates are based primarily on the opinions of physicians interviewed in each of the seven markets; our estimates are also compatible with trends observed in sales data for MS drugs. Drug-treatment rates will rise over the forecast period as physicians, especially general neurologists, become more accustomed to prescribing disease-modifying agents and using new diagnostic tools and criteria. The arrival of emerging therapies, many with convenient oral dosing formulations, will increase the likelihood of patients receiving and continuing drug therapy. As a result of the launch of these drugs and the relaunch of natalizumab, the percentage of patients whose disease is refractory to or who had abandoned IFN-β therapy will decline as many of these patients resume treatment. The expanding use of disease-modifying drugs in SP-MS patients with relapses and early-stage MS patients (those who have experienced only one demyelinating event) will also contribute to an increase in the number of patients who are drug-treated. Use of emerging therapies in nonrelapsing SP-MS patients and PP-MS patients will increase the drug-treated patient population as well.

Agents Included in Our Market Analysis

Our market tables specify prominent agents and the sales we forecast for them. In some cases, agents with a small share of sales are grouped together. Here, we define the specific agents that make up the subgroups shown in our market tables.

Other corticosteroids: oral prednisone.

Betaseron: 250 mcg, 500 mcg (launch in 2009).

Rebif: 22 mcg, 44 mcg (standard), 44 mcg (new formulation, launch in 2007).

Glatiramer acetate: 20 mg, 40 mg (launch in 2009).

Where appropriate, supported by recent trial, patent extension, or pricing/reimbursement information as well as current expert opinion, we adjusted assumptions made in previous forecasts; we provide in Chapter 9, "Market Outlook," our detailed explanation of any assumption changes.

General Statements About Pricing

We calculate the price per day of each drug class based on a sample of the most frequently prescribed agents, as identified through our physician interviews, prescribing surveys, and other data sources. All prices are based on ex-manufacturer prices as reported by IMS.

In rare cases, we obtain prices from country-specific pricing publications and Web sites. In those cases, we back-calculate prices to the ex-manufacturer level (not including rebates). For European country and Japanese pricing, we apply discount rates to back-calculate ex-manufacturer pricing. To determine the appropriate discount for each country, we rely on two sources: (1) the surveys published by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and (2) discount rates published by IMS Health. The EFPIA surveys generate country-specific estimates of discount rates between manufacturer, wholesaler, and pharmacy pricing in the European markets. The IMS discount rates are generated using data collected during IMS's audit process at all levels of the distribution chain. We then calculate the price per day by multiplying the price per unit by the number of units administered per day. Estimates do not include inflationary pricing.

For retail products, the following discount rates are applied to retail pricing to estimate ex-manufacturer prices.

Discount Rates

	Discount rates applied to retail product prices	Discount rates applied to hospital product prices	Currency exchange rates[a]
France	40%	0%	0.81
Germany	46%	0%	0.81
Italy	39%	50%	0.81
Spain	37%	37%	0.81
United Kingdom	25%	25%	0.55
Japan	18%	18%	109

a. Exchanges rates: Dollar:Euro (France, Germany, Italy, Spain), Dollar:British Pound (United Kingdom), Dollar: Japanese Yen (Japan)

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Source: Decision Resources, Inc.

Pricing Assumptions

The launch price of natalizumab in 2005, prior to its withdrawal early that year, of more than $55/day becomes our base-year price for the drug in the United States. When natalizumab was relaunched in 2006 in the United States, it was priced at a 30% premium over its original launch price, and

we use this increased price in our 2010, 2015, and 2020 forecast years. The launch prices in Europe take this increase into account and reflect country-specific discounts of 10-20% of the price of the agent in the United States. In Japan, the launch price of natalizumab is based on a 10% premium on the U.S. price.

Japanese Price Adjustments

To account for the biennial pharmaceutical price cuts mandated by the Japanese Ministry of Health, Labor, and Welfare, we applied the following cuts to the price of Japanese agents:

- 7% for long-listed drugs (those agents whose patents have expired and generics are available): Methotrexate, azathioprine, cyclophosphamide, prednisone, methylprednisolone.
- 2% for new agents (those agents available on the Japanese market for less than two years) and agents that do not have marketed competing products in the same drug class: Avonex, mitoxantrone, natalizumab, FTY-720.
- 4% for all other agents: Betaseron.

Dosing, Days of Therapy, and Compliance

For disease-modifying therapies, including IFN-β drugs and glatiramer acetate, we assume a 90% compliance rate based on statements of experts interviewed. Experts say that because MS is a serious and debilitating disease, most patients are highly compliant.

For therapies that require intravenous administration, such as mitoxantrone, methylprednisolone and other corticosteroids, cyclophosphamide, natalizumab, daclizumab, and MBP-8298, we assume 98% compliance because administration takes place in a hospital.

For the oral immunosuppressant mycophenolate mofetil, we assume 70% compliance. Patients are likely to be less compliant because of the chronic severe suppression of the immune system associated with this drug.

For oral therapies that are adjuncts to main therapy, we assume a slightly lower compliance rate of 80% compared with compliance to main therapies. Patients will likely be less compliant with a daily drug therapy that is not the primary component of their drug regimen.

Other emerging agents have oral formulations, including teriflunomide, cladribine, FTY-720, BG-12, and laquinimod. We assume a compliance rate of 95% because patients will likely be more compliant and persistent with an oral therapy than with injectables.

Except for the corticosteroids, all therapies are chronic and therefore have an optimal 365 days of therapy per year. Although four- to five-day pulse therapy of oral cladribine is being tested (ONWARD study, see Chapter 6, "Emerging Oral Immunomodulatory Therapies," for more information), in the absence of data from the trial, we assume 365 days of therapy. Corticosteroids are typically used during exacerbations. Methylprednisolone

is typically prescribed for 5 days of continuous therapy and can be followed by other corticosteroids for 14 days.

Generic Erosion

We have reduced the prices of drugs with patents expiring during our forecast period to account for generics competition; the percentage share of prescriptions shifting to generics has been adjusted to reflect the strength of the overall generic drug market in each country as established by a generics erosion analogue model.

Chemotherapeutic agents including methotrexate and cyclophosphamide, the immunosuppressant azathioprine, and corticosteroids methylprednisolone and prednisone will experience generics competition during this forecast period. Although mitoxantrone lost its patent in oncology indications in April 2006, the MS indication is protected by an orphan-drug status designation until October 2007. In estimating generic patient share, we assume that when generics become available for oncology indications, some physicians will use generic mitoxantrone to treat MS patients.

We assume that in the United States in 2010, 2015, and 2020, the price of generic mitoxantrone will be 30%, 20%, and 15% of the brand price, respectively. We assume that there will be no change to the prices of generic methotrexate, azathioprine, cyclophosphamide, methylprednisolone, and prednisone in the United States during our forecast period.

We assume varying levels of generic price erosion in each of the European markets. We assume that in France in 2010, 2015, and 2020, the prices of generic azathioprine and prednisone will not change from the base year. In France in 2010, 2015, and 2020, the price of generic mitoxantrone will be 70%, 60%, and 50% of the brand price, respectively, while the prices of generic methotrexate, cyclophosphamide, and methylprednisolone will be 75% of the respective brand price in all forecast years.

We assume that in Germany, the prices of generic mitoxantrone, methotrexate, azathioprine, and prednisone will not change during our forecast period; in each forecast year, the prices of generic cyclophosphamide and methylprednisolone will be 50% of the respective brand price.

We assume that in Italy the price of generic mitoxantrone, azathioprine, methylprednisolone, and prednisone will not change during our forecast period; in all forecast years, the prices of generic methotrexate and cyclophosphamide will be 75% of the respective brand price.

In Spain in 2010, 2015, and 2020, we assume that the price of generic mitoxantrone will be 70%, 60%, and 50% of the brand price, respectively. We assume that in Spain, the prices of generic methotrexate, azathioprine, cyclophosphamide, methylprednisolone, and prednisone will be 75% of the respective brand price for all forecast years.

We also assume that in the United Kingdom, the generic price of mitoxantrone, methotrexate, azathioprine, methylprednisolone, and

prednisone will not change during our forecast period; in 2010, 2015, and 2020, the generic price of cyclophosphamide will be 50% of the brand price.

We assume that in Japan, the prices of generic methotrexate and methylprednisolone will not change during our forecast period. We assume that in Japan in 2010, 2015, and 2020, the price of generic mitoxantrone, azathioprine, cyclophosphamide, and prednisone will be 80% of the respective brand price.

We then assume that in the United States in 2010, 2015, and 2020, the generic form of mitoxantrone will obtain 40%, 70%, and 85% of patient share, respectively. The generic forms of methotrexate, azathioprine, methylprednisolone, and prednisone will obtain 90%, 70%, 2%, and 98% of patient share in the United States in all forecast years, respectively. In the United States in 2010, 2015, and 2020, the generic form of cyclophosphamide will obtain 10%, 20%, and 30% of patient share, respectively.

We assume the following patient shares in Europe and Japan for generic forms of these drugs:

Patient Shares

Compound	2010	2015	2020
Europe[a]			
Mitoxantrone	10-55%	15-60%	20-65%
Methotrexate	25-80%	30-80%	35-80%
Azathioprine	15-70%	30-70%	40-70%
Cyclophosphamide	15-60%	30-60%	40-75%
Methylprednisolone	5-60%	15-70%	20-80%
Prednisone	15-75%	30-80%	40-80%
Japan			
Mitoxantrone	5%	15%	20%
Methotrexate	3%	5%	10%
Azathioprine	25%	30%	35%
Cyclophosphamide	5%	15%	25%
Methylprednisolone	9%	14%	17%
Prednisone	75%	80%	83%

a. The volume share of the generic form in Europe varies by country according to Decision Resources' generic erosion model.

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Source: Decision Resources, Inc.

We assume that in the United States in 2015, the generic price of glatiramer acetate will be 70% of the brand price; in 2020, the generic price of glatiramer acetate in the United States will be 20% of the brand price. In Europe in 2015, we assume that the generic price of glatiramer acetate will be 65-80% of the brand price; in 2020, the generic price of glatiramer acetate will be 30-50% of the brand price.

We then assume that in the United States in 2015, the generic form of glatiramer acetate will obtain 40% of all MS patient share; it will obtain 80% of patient share in 2020. We assume that in Europe in 2015, the generic form of glatiramer acetate will obtain 10% of patient share in France; 30% in Germany, Italy, and Spain; and 40% in the United Kingdom. In Europe in 2020, the generic form of glatiramer acetate will obtain 60% of the patient share in France, 80% in Germany, 55% in Italy and Germany, and 75% in the United Kingdom.

We assume that in the United States in 2015, the price of biogeneric Betaseron will be 65% of the brand price; in 2020, the price of biogeneric Betaseron will be 50%. In the United States in 2015, the price of biogeneric Avonex and Rebif will be 70% of the respective brand price. In the United States in 2020, we assume that the priee of biogeneric Avonex and Rebif will be 55% of their respective brand prices. We then assume that in the United States in 2015, the generic form of Betaseron will have a 30% patient share, and the generic forms of Avonex and Rebif will each have a 25% patient share. In the United States in 2020, we assume that the generic form of Betaseron will have a 50% patient share, Avonex 45%, and Rebif 45%.

We assume that in Europe in 2010, 2015, and 2020, the prices of biogeneric Betaseron and Avonex will be 80%, 70%, and 60% of their brand prices, respeetively. We assume that in Europe in 2015, the price of biogeneric Rebif will be 80% of the brand price, and in 2020, it will be 70% of the brand price.

We then assume in 2010, the generic forms of Betaseron and Avonex will have a 20% patient share in France, Italy, and Spain and a 25% patient share in Germany and the United Kingdom. In Europe in 2015, we assume the generic forms of Betaseron and Avonex will have a 45% patient share in France, Italy, and Spain and 50% in Germany and the United Kingdom. In Europe in 2020, we assume the generic forms will have a 60% patient share in the United Kingdom and 50% in all other European markets. We also assume that in Europe in 2015, the generic form of Rebif will have a 20% patient share in France, Italy, and Spain, while the share of generic Rebif will be 25% in the United Kingdom in 2015. In Europe in 2020, the generic form of Rebif will have a 45% patient share in France, Italy, and Spain; generic Rebif will have a 50% patient share in Germany and the United Kingdom.

We assume that in the United States in 2010, 2015, and 2020, the generic price of mycophenolate mofetil will be 70%, 30%, and 15% of the brand price, respectively. We also assume that the generic form of mycophenolate mofetil will have a 75%, 25%, and 15% patient share in 2010, 2015, and 2020, respectively.

We assume that in France in 2015, the price of generic mycophenolate mofetil will be 50% of the brand price; in 2020, it will be 30%. In Germany in 2015 and 2020, we assume the price of generic mycophenolate mofetil will be 40% and 25% of the brand price, respectively. We assume the price of generic mycophenolate mofetil will be 55% of the brand price in Italy in 2015 and 40% in 2020. In Spain in 2010, 2015, and 2020, we assume that the price of generic mycophenolate mofetil will be 60%, 55%, and 50% of the

brand price, respectively, while in the United Kingdom the price will be 95%, 65%, and 45% of the brand price, respectively.

We assume that in France in 2015, generic mycophenolate mofetil will have a 50% patient share; in 2020, it will have 70%. In Germany, the generic form will have a 70% patient share in 2015 and 80% in 2020. We assume that in Italy, the generic form of mycophenolate mofetil will have a 50% patient share in 2015 and 55% in 2020. In Spain in 2010, 2015, and 2020, we assume generic mycophenolate mofetil will have a 25%, 55%, and 60% patient share, respectively. We assume that in the United Kingdom in 2010, the generic form of mycophenolate mofetil will not have any patient share; mycophenolate mofetil loses patent protection in the United Kingdom in 2010, but it is unlikely to experience generic competition during this forecast year. We assume that in the United Kingdom in 2015, mycophenolate mofetil will have a 50% patient share and in 2020, a 75% patient share.

We assume that in Japan in 2015, the price of generic mycophenolate mofetil will be 47% of the brand price; in 2020, it will be 30%. In Japan in 2015, we assume that generic mycophenolate mofetil will have a 15% patient share; in 2020, a 25% patient share.

Only one emerging therapy will experience generic competition during our forecast period. We anticipate that FTY-720 (Novartis/Mitsubishi Pharma's fingolimod) will be granted a five-year Hatch-Waxman patent extension in the United States. Therefore, the generic form of FTY-720 will enter the U.S. market in 2019 and be priced at 85% of the brand price. FTY-720 will continue to have market exclusivity in Europe through the end of our study period and so will not experience generic competition until after 2020.

Emerging Therapy Prices

Daclizumab will receive approval for MS three years after the relaunch of natalizumab in 2006. Daclizumab's price is the price of branded Zenapax.

MBP-8298 will be the only novel altered peptide ligand on the market during our forecast period. We have priced this drug similar to the most expensive IFN-β (Rebif) because it is efficacious in only a small patient population; therefore, BioMS Medical will have to price the drug at a premium to compensate for the size of the population.

Cladribine will be the first oral immunosuppressant on the market; launch is expected in early 2010. We have priced cladribine at a 10% premium over the most expensive IFN-β (Rebif); because of cladribine's modest efficacy and potential for severe side effects, we do not price it at more than a 10% premium despite the convenience of an oral formulation that is administered in two multiday doses per year. Teriflunomide, which will launch after cladribine in 2011, is priced to match cladribine because it has an oral formulation and modest efficacy but has a severe side-effect profile. We have priced both BG-12 and laquinimod similar to teriflunomide and cladribine because these drugs have also demonstrated modest efficacy and safety and have oral formulations; they will compete with each other for patient share.

We priced FTY-720 similar to natalizumab's original launch price. Although FTY-720 will not be the first oral MS therapy to reach the market, it will command a higher price than that of other emerging therapies because of its superior efficacy. In addition, because it has both an oral formulation and excellent efficacy, we expect it to be priced higher than current therapies--the exception is natalizumab, which is more efficacious. Similar to that of natalizumab, the launch priees of FTY-720 in Europe reflect country-specific discounts of 10-20% of the price of the agent in the United States.

A higher-dose formulation of Betaseron (500 mcg) is expected to launch in 2009. We have priced the 500 mcg dose of Betaseron in the United States at a 15% premium over the current price of the drug. The higher-dose formulation appears as safe as the current 250 mcg dose, although whether its efficacy is improved is unclear; we expect that by 2020, the 500 mcg dose will be used by 80% of U.S. patients receiving Betaseron. In Europe, 500 mcg Betaseron will receive a 10% premium over the current price of the drug in each market, and by 2020, it will receive 45%-65% of total Betaseron usage. We have weighted the prices and usages of both doses of Betaseron in our market analysis.

We have priced the reformulation of Rebif at a 15% premium over the current cost of Rebif in the United States and at a 10% premium over the existing price of Rebif in each of the five European markets. Because the new formulation appears to have a safer side-effect profile, we expect it to be used extensively in the U.S. and European markets following its launch in 2007 (80% and 45-70% of total Rebif use in 2020, respectively) at the expense of the current formulation of Rebif. We have weighted the prices and usage of both formulations of Rebif in our market analysis.

The higher-dose formulation of glatiramer acetate (40 mg) is also expected to launch during our study period (in 2009 in the U.S. and European markets). As we did with the new formulation of Rebif, we have priced this new dose of glatiramer acetate at a 15% premium over the current price of glatiramer acetate in the United States and applied a 10% premium over the cost of the drug in all European markets. We expect this new strength of glatiramer acetate to enjoy significant uptake in the United States (80%) and Europe (45-65%) by 2020. Similar to our market analysis of Rebif, we have weighted the price and drug usage of both strengths of glatiramer acetate in our market analysis.

Because of the chronic nature of MS therapies, we assume that the number of optimal treated days for all emerging therapies is 365. We assume that compliance rates for daclizumab and MBP-8298, which are administered via infusion and therefore will have high compliance rates, to be 98%. We assume compliance rates for the oral therapies, including teriflunomide, cladribine, FTY-720, BG-12, and laquinimod, to be higher than with current injectable therapies (90% compliance) and so assume 95% compliance for these agents.

Table B-1

Assumptions Behind the 2005 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
United States	197					
Recombinant interferons		75.3	148	329	37.89	1,845.3
IFN-β-1b		17.9	35	329	34.51	399.4
IFN-β-1a (Avonex)		42.9	85	329	36.90	1,024.9
IFN-β-1a (Rebif)		14.5	28	329	45.00	421.0
Altered peptide ligands		33.1	65	329	37.71	807.8
Glatiramer acetate		33.1	65	329	37.71	807.8
MBP-8298		—	—	—	—	—
Chemotherapeutics		7.3	14	351	7.52	38.6
Mitoxantrone		3.9	8	358	13.52	37.1
Cyclophosphamide		2.6	5	358	0.74	1.4
Methotrexate		0.8	1	292	0.24	0.1
Oral immunosuppressants		2.5	5	288	4.03	5.5
Azathioprine		2.3	4	292	2.30	3.0
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		0.3	1	256	19.40	2.5
Monoclonal antibodies		0.5	1	358	56.75	21.9
Natalizumab		0.5	1	358	56.75	21.9
Daclizumab		—	—	—	—	—
Corticosteroids		39.0	77	7	6.41	2.4
Methylprednisolone		28.0	55	5	8.89	2.4
Other corticosteroids		11.0	22	14	0.10	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
France	25					
Recombinant interferons		70.7	18	329	37.73	223.0
IFN-β-1b		16.1	4	329	37.47	50.6
IFN-β-1a (Avonex)		34.1	9	329	37.55	107.2
IFN-β-1a (Rebif)		20.4	5	329	38.22	65.3
Altered peptide ligands		11.4	3	329	35.96	34.4
Glatiramer acetate		11.4	3	329	35.96	34.4
MBP-8298		—	—	—	—	—
Chemotherapeutics		10.2	3	338	2.10	2.0
Mitoxantrone		5.2	1	358	3.86	1.8
Cyclophosphamide		2.0	N.M.	358	0.56	0.1
Methotrexate		3.1	1	292	0.10	N.M.

(continued)

Table B-1 (cont.)

Assumptions Behind the 2005 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/Day ($)	Sales ($MM)
Oral immunosuppressants		7.7	2	278	5.55	2.8
Azathioprine		4.8	1	292	1.09	0.4
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		2.9	1	256	12.84	2.4
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		34.7	9	7	19.19	0.8
Methylprednisolone		27.4	7	5	24.20	0.8
Other corticosteroids		7.4	2	14	0.54	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Germany	**44**					
Recombinant interferons		70.3	31	329	47.16	475.1
IFN-β-1b		24.8	11	329	43.40	154.2
IFN-β-1a (Avonex)		21.1	9	329	43.27	130.5
IFN-β-1a (Rebif)		24.5	11	329	54.32	190.4
Altered peptide ligands		20.3	9	329	40.82	118.5
Glatiramer acetate		20.3	9	329	40.82	118.5
MBP-8298		—	—	—	—	—
Chemotherapeutics		12.1	5	348	2.37	4.4
Mitoxantrone		7.5	3	358	3.60	4.2
Cyclophosphamide		2.8	1	358	0.45	0.2
Methotrexate		1.8	1	292	0.16	N.M.
Oral immunosuppressants		6.0	3	292	2.20	1.7
Azathioprine		6.0	3	292	2.20	1.7
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		44.4	19	7	21.87	2.1
Methylprednisolone		35.4	15	5	27.35	2.1
Other corticosteroids		9.0	4	14	0.36	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-1 (cont.)

Assumptions Behind the 2005 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/Day ($)	Sales ($MM)
Italy	22					
Recombinant interferons		63.9	14	329	38.81	179.2
IFN-β-1b		15.6	3	329	34.38	38.7
IFN-β-1a (Avonex)		21.1	5	329	33.98	51.8
IFN-β-1a (Rebif)		27.2	6	329	45.07	88.7
Altered peptide ligands		9.6	2	329	31.12	21.7
Glatiramer acetate		9.6	2	329	31.12	21.7
MBP-8298		—	—	—	—	—
Chemotherapeutics		11.1	2	331	0.88	0.8
Mitoxantrone		4.5	1	358	1.98	0.7
Cyclophosphamide		2.0	N.M.	358	0.23	N.M.
Methotrexate		4.5	1	292	0.06	N.M.
Oral immunosuppressants		5.7	1	292	0.89	0.3
Azathioprine		5.7	1	292	0.89	0.3
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		37.0	8	7	12.52	0.5
Methylprednisolone		29.4	6	5	15.65	0.5
Other corticosteroids		7.7	2	14	0.52	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Spain	13					
Recombinant interferons		83.9	11	329	42.89	156.2
IFN-β-1b		33.3	4	329	38.58	55.7
IFN-β-1a (Avonex)		23.0	3	329	37.88	37.8
IFN-β-1a (Rebif)		27.6	4	329	52.23	62.7
Altered peptide ligands		7.4	1	329	35.30	11.4
Glatiramer acetate		7.4	1	329	35.30	11.4
MBP-8298		—	—	—	—	—
Chemotherapeutics		4.2	1	331	2.17	0.4
Mitoxantrone		1.5	N.M.	358	5.86	0.4
Cyclophosphamide		1.0	N.M.	358	0.19	N.M.
Methotrexate		1.7	N.M.	292	0.02	N.M.

(continued)

Table B-1 (cont.)

Assumptions Behind the 2005 Multiple Sclerosis Market (All Populations)	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/Day ($)	Sales ($MM)
Oral immunosuppressants		4.4	1	292	0.57	0.1
Azathioprine		4.4	1	292	0.57	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		30.8	4	7	8.72	0.2
Methylprednisolone		23.4	3	5	11.33	0.2
Other corticosteroids		7.3	1	14	0.35	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
United Kingdom	11					
Recombinant interferons		18.4	2	329	40.46	27.7
IFN-β-1b		5.7	1	329	31.69	6.7
IFN-β-1a (Avonex)		5.0	1	329	37.95	7.1
IFN-β-1a (Rebif)		7.7	1	329	48.56	13.9
Altered peptide ligands		11.5	1	329	30.99	13.2
Glatiramer acetate		11.5	1	329	30.99	13.2
MBP-8298		—	—	—	—	—
Chemotherapeutics		4.4	N.M.	341	1.25	0.2
Mitoxantrone		2.3	N.M.	358	2.22	0.2
Cyclophosphamide		1.0	N.M.	358	0.37	N.M.
Methotrexate		1.1	N.M.	292	0.08	N.M.
Oral immunosuppressants		1.1	N.M.	292	1.35	0.1
Azathioprine		1.1	N.M.	292	1.35	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		60.0	7	8	13.66	0.5
Methylprednisolone		42.1	5	5	19.34	0.5
Other corticosteroids		17.9	2	14	0.30	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
8G-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-1 (cont.)

Assumptions Behind the 2005 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
Japan	3					
Recombinant interferons		74.1	3	329	42.75	35.8
IFN-β-1b		74.1	3	329	42.75	35.8
IFN-β-1a (Avonex)		—	—	—	—	—
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		4.7	N.M.	344	2.18	0.1
Mitoxantrone		2.4	N.M.	358	3.95	0.1
Cyclophosphamide		1.4	N.M.	358	0.54	N.M.
Methotrexate		1.0	N.M.	292	0.23	N.M.
Oral immunosuppressants		4.0	N.M.	292	4.21	0.2
Azathioprine		4.0	N.M.	292	4.21	0.2
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		64.5	2	8	30.78	0.3
Methylprednisolone		44.7	2	5	44.39	0.3
Other corticosteroids		19.8	1	14	—	—
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-2

Assumptions Behind the 2010 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
United States	210					
Recombinant interferons		70.4	148	329	39.15	1,904.5
IFN-β-1b		14.9	31	329	35.03	360.8
IFN-β-1a (Avonex)		38.3	81	329	36.90	976.2
IFN-β-1a (Rebif)		17.2	36	329	47.71	567.5
Altered peptide ligands		29.6	62	329	38.28	783.4
Glatiramer acetate		29.6	62	329	38.28	783.4
MBP-8298		—	—	—	—	—
Chemotherapeutics		5.4	11	354	6.27	25.2
Mitoxantrone		3.3	7	358	9.73	24.2
Cyclophosphamide		1.8	4	358	0.73	1.0
Methotrexate		0.3	1	292	0.24	N.M.
Oral immunosuppressants		2.3	5	306	19.51	31.0
Azathioprine		1.3	3	292	2.30	1.8
Teriflunomide		—	—	—	—	—
Cladribine		0.7	2	347	49.50	26.6
Mycophenolate mofetil		0.3	1	256	17.95	2.5
Monoclonal antibodies		5.7	12	358	59.33	254.0
Natalizumab		4.0	8	358	72.64	216.0
Daclizumab		1.7	4	358	29.06	38.0
Corticosteroids		38.0	80	7	6.52	2.6
Methylprednisolone		27.7	58	5	8.89	2.5
Other corticosteroids		10.2	21	14	0.10	N.M.
Oral immunomodulators		1.5	3	347	55.00	59.2
FTY-720		1.5	3	347	55.00	59.2
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
France	27					
Recombinant interferons		69.1	18	329	37.17	224.9
IFN-β-1b		13.0	3	329	36.24	41.3
IFN-β-1a (Avonex)		33.2	9	329	36.05	105.0
IFN-β-1a (Rebif)		22.8	6	329	39.33	78.6
Altered peptide ligands		15.9	4	329	36.14	50.2
Glatiramer acetate		15.9	4	329	36.14	50.2
MBP-8298		—	—	—	—	—
Chemotherapeutics		8.4	2	343	2.21	1.8
Mitoxantrone		4.6	1	358	3.75	1.7
Cyclophosphamide		1.9	N.M.	358	0.54	0.1
Methotrexate		1.9	N.M.	292	0.09	N.M.

(continued)

Table B-2 (cont.)

Assumptions Behind the 2010 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		8.3	2	284	9.62	6.4
Azathioprine		4.6	1	292	1.05	0.4
Teriflunomide		—	—	—	—	—
Cladribine		0.8	N.M.	347	47.47	3.4
Mycophenolate mofetil		3.0	1	256	12.84	2.6
Monoclonal antibodies		3.3	1	358	69.29	22.1
Natalizumab		3.3	1	358	69.29	22.1
Daclizumab		—	—	—	—	—
Corticosteroids		34.7	9	7	17.76	0.8
Methylprednisolone		27.3	7	5	22.39	0.8
Other corticosteroids		7.3	2	14	0.51	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Germany	48					
Recombinant interferons		69.5	33	329	46.82	508.0
IFN-β-1b		21.2	10	329	41.55	137.7
IFN-β-1a (Avonex)		21.9	10	329	41.11	140.3
IFN-β-1a (Rebif)		26.4	13	329	55.77	230.0
Altered peptide ligands		17.0	8	329	41.02	108.6
Glatiramer acetate		17.0	8	329	41.02	108.6
MBP-8298		—	—	—	—	—
Chemotherapeutics		9.6	5	353	2.28	3.7
Mitoxantrone		6.5	3	358	3.23	3.6
Cyclophosphamide		2.4	1	358	0.36	0.1
Methotrexate		0.7	N.M.	292	0.16	N.M.
Oral immunosuppressants		5.6	3	300	9.13	8.1
Azathioprine		4.8	2	292	2.19	1.5
Teriflunomide		—	—	—	—	—
Cladribine		0.8	N.M.	347	51.84	6.6
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		3.3	2	358	75.64	42.8
Natalizumab		3.3	2	358	75.64	42.8
Daclizumab		—	—	—	—	—
Corticosteroids		44.3	21	7	15.38	1.6
Methylprednisolone		35.4	17	5	19.15	1.6
Other corticosteroids		8.9	4	14	0.34	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-2 (cont.)

Assumptions Behind the 2010 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Italy	24					
Recombinant interferons		63.6	15	329	38.66	190.3
IFN-β-1b		13.2	3	329	33.25	34.0
IFN-β-1a (Avonex)		22.4	5	329	32.62	56.5
IFN-β-1a (Rebif)		28.0	7	329	46.05	99.7
Altered peptide ligands		11.6	3	329	31.27	28.1
Glatiramer acetate		11.6	3	329	31.27	28.1
MBP-8298		—	—	—	—	—
Chemotherapeutics		7.6	2	339	0.99	0.6
Mitoxantrone		3.6	1	358	1.94	0.6
Cyclophosphamide		1.8	N.M.	358	0.22	N.M.
Methotrexate		2.2	1	292	0.06	N.M.
Oral immunosuppressants		5.2	1	300	8.79	3.7
Azathioprine		4.4	1	292	0.87	0.3
Teriflunomide		—	—	—	—	—
Cladribine		0.8	N.M.	347	52.36	3.4
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		2.6	1	358	76.19	16.7
Natalizumab		2.6	1	358	76.19	16.7
Daclizumab		—	—	—	—	—
Corticosteroids		37.2	9	7	12.35	0.5
Methylprednisolone		29.6	7	5	15.44	0.5
Other corticosteroids		7.6	2	14	0.29	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Spain	14					
Recombinant interferons		82.2	11	329	42.64	159.2
IFN-β-1b		29.7	4	329	37.31	50.3
IFN-β-1a (Avonex)		23.8	3	329	36.37	39.3
IFN-β-1a (Rebif)		28.7	4	329	53.32	69.6
Altered peptide ligands		9.7	1	329	35.48	15.6
Glatiramer acetate		9.7	1	329	35.48	15.6
MBP-8298		—	—	—	—	—
Chemotherapeutics		3.2	N.M.	348	2.54	0.4
Mitoxantrone		1.7	N.M.	358	4.63	0.4
Cyclophosphamide		1.0	N.M.	358	0.17	N.M.
Methotrexate		0.5	N.M.	292	0.02	N.M.

(continued)

Table B-2 (cont.)

Assumptions Behind the 2010 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		4.0	1	303	9.51	1.8
Azathioprine		3.2	N.M.	292	0.54	0.1
Teriflunomide		—	—	—	—	—
Cladribine		0.8	N.M.	347	47.14	1.7
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		2.5	N.M.	358	68.28	8.6
Natalizumab		2.5	N.M.	358	68.28	8.6
Daclizumab		—	—	—	—	—
Corticosteroids		30.8	4	7	8.44	0.2
Methylprednisolone		23.5	3	5	10.97	0.2
Other corticosteroids		7.3	1	14	0.33	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
United Kingdom	22					
Recombinant interferons		24.8	5	329	38.83	68.8
IFN-β-1b		5.8	1	329	29.44	12.1
IFN-β-1a (Avonex)		8.6	2	329	34.91	21.5
IFN-β-1a (Rebif)		10.4	2	329	47.24	35.2
Altered peptide ligands		12.6	3	329	29.97	26.9
Glatiramer acetate		12.6	3	329	29.97	26.9
MBP-8298		—	—	—	—	—
Chemotherapeutics		3.0	1	345	1.09	0.2
Mitoxantrone		1.4	N.M.	358	2.12	0.2
Cyclophosphamide		1.0	N.M.	358	0.26	N.M.
Methotrexate		0.6	N.M.	292	0.08	N.M.
Oral immunosuppressants		1.0	N.M.	292	1.13	0.1
Azathioprine		1.0	N.M.	292	1.13	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		2.6	1	358	68.68	14.0
Natalizumab		2.6	1	358	68.68	14.0
Daclizumab		—	—	—	—	—
Corticosteroids		51.9	11	7	13.66	0.8
Methylprednisolone		38.8	8	5	18.18	0.8
Other corticosteroids		13.1	3	14	0.32	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-2 (cont.)

Assumptions Behind the 2010 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Japan	4					
Recombinant interferons		73.1	3	329	43.25	40.6
IFN-β-1b		62.0	2	329	42.75	34.0
IFN-β-1a (Avonex)		11.1	N.M.	329	46.01	6.6
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		3.6	N.M.	340	1.44	0.1
Mitoxantrone		1.4	N.M.	358	3.23	0.1
Cyclophosphamide		1.3	N.M.	358	0.44	N.M.
Methotrexate		1.0	N.M.	292	0.22	N.M.
Oral immunosuppressants		3.0	N.M.	292	3.43	0.1
Azathioprine		3.0	N.M.	292	3.43	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		58.6	2	7	24.95	0.3
Methylprednisolone		41.7	2	5	35.03	0.3
Other corticosteroids		16.9	1	14	—	—
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-3

Assumptions Behind the 2015 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
United States	225					
Recombinant interferons		56.9	128	329	38.98	
IFN-β-1b		12.3	28	329	36.61	332.0
IFN-β-1a (Avonex)		26.5	60	329	34.13	668.1
IFN-β-1a (Rebif)		18.1	41	329	47.71	636.2
Altered peptide ligands		20.7	47	333	40.52	628.1
Glatiramer acetate		17.9	40	329	39.80	524.3
MBP-8298		2.9	6	358	45.00	103.8
Chemotherapeutics		4.6	10	354	3.88	14.3
Mitoxantrone		2.8	6	358	5.95	13.4
Cyclophosphamide		1.5	3	358	0.73	0.9
Methotrexate		0.3	1	292	0.24	N.M.
Oral immunosuppressants		5.8	13	326	35.48	159.0
Azathioprine		1.3	3	292	2.30	1.9
Teriflunomide		1.0	2	347	49.50	38.6
Cladribine		3.0	7	347	49.50	115.7
Mycophenolate mofetil		0.5	1	256	9.22	2.8
Monoclonal antibodies		7.9	18	358	58.91	375.4
Natalizumab		5.4	12	358	72.93	316.2
Daclizumab		2.5	6	358	29.06	59.2
Corticosteroids		36.7	82	7	6.62	2.7
Methylprednisolone		27.2	61	5	8.89	2.7
Other corticosteroids		9.5	21	14	0.10	N.M.
Oral immunomodulators		13.3	30	347	54.39	561.7
FTY-720		11.8	26	347	55.00	505.2
BG-12		0.7	2	347	49.50	28.2
Laquinimod		0.7	2	347	49.50	28.2
France	28					
Recombinant interferons		58.9	16	329	36.48	197.1
IFN-β-1b		9.8	3	329	36.61	32.9
IFN-β-1a (Avonex)		24.6	7	329	33.61	76.0
IFN-β-1a (Rebif)		24.5	7	329	39.31	88.3
Altered peptide ligands		15.6	4	332	36.55	52.9
Glatiramer acetate		13.5	4	329	36.64	45.4
MBP-8298		2.1	1	358	36.00	7.5
Chemotherapeutics		6.3	2	351	2.44	1.5
Mitoxantrone		4.0	1	358	3.63	1.4
Cyclophosphamide		1.7	N.M.	358	0.52	0.1
Methotrexate		0.7	N.M.	292	0.09	N.M.

(continued)

Table B-3 (cont.)

Assumptions Behind the 2015 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		9.7	3	299	18.97	17.1
Azathioprine		3.6	1	292	1.00	0.3
Teriflunomide		1.0	N.M.	347	47.47	4.6
Cladribine		2.2	1	347	47.47	10.2
Mycophenolate mofetil		3.0	1	256	9.63	2.0
Monoclonal antibodies		6.1	2	358	61.23	37.5
Natalizumab		4.1	1	358	69.56	28.7
Daclizumab		2.0	1	358	44.03	8.8
Corticosteroids		34.7	10	7	17.51	0.8
Methylprednisolone		27.3	8	5	22.08	0.8
Other corticosteroids		7.3	2	14	0.48	N.M.
Oral immunomodulators		10.6	3	347	48.35	49.6
FTY-720		9.0	3	347	48.50	42.5
BG-12		0.8	N.M.	347	47.47	3.6
Laquinimod		0.8	N.M.	347	47.47	3.6
Germany	52					
Recombinant interferons		58.4	30	329	45.72	456.8
IFN-β-1b		14.7	8	329	41.77	104.9
IFN-β-1a (Avonex)		18.6	10	329	36.78	116.9
IFN-β-1a (Rebif)		25.1	13	329	54.64	235.0
Altered peptide ligands		16.6	9	332	40.25	115.7
Glatiramer acetate		14.4	8	329	40.64	100.3
MBP-8298		2.2	1	358	37.69	15.4
Chemotherapeutics		7.1	4	355	2.13	2.8
Mitoxantrone		4.8	3	358	2.98	2.7
Cyclophosphamide		2.0	1	358	0.32	0.1
Methotrexate		0.2	N.M.	292	0.16	N.M.
Oral immunosuppressants		6.8	4	318	25.98	31.5
Azathioprine		3.5	2	292	2.19	1.2
Teriflunomide		1.0	1	347	51.84	9.4
Cladribine		2.2	1	347	51.84	21.0
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		6.0	3	358	63.50	71.5
Natalizumab		4.0	2	358	75.84	57.2
Daclizumab		2.0	1	358	38.55	14.4
Corticosteroids		44.3	23	7	14.31	1.6
Methylprednisolone		35.5	18	5	17.78	1.6
Other corticosteroids		8.8	5	14	0.31	N.M.
Oral immunomodulators		9.6	5	347	53.05	92.1
FTY-720		8.1	4	347	53.28	77.8
BG-12		0.8	N.M.	347	51.84	7.1
Laquinimod		0.8	N.M.	347	51.84	7.1

(continued)

Table B-3 (cont.)

Assumptions Behind the 2015 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
Italy	25					
Recombinant interferons		59.2	15	329	38.57	184.0
IFN-β-1b		10.7	3	329	33.28	28.6
IFN-β-1a (Avonex)		19.2	5	329	30.41	47.1
IFN-β-1a (Rebif)		29.3	7	329	45.85	108.3
Altered peptide ligands		11.4	3	333	32.28	30.3
Glatiramer acetate		9.5	2	329	30.69	23.6
MBP-8298		1.9	N.M.	358	40.28	6.7
Chemotherapeutics		5.3	1	344	1.00	0.5
Mitoxantrone		2.6	1	358	1.93	0.4
Cyclophosphamide		1.7	N.M.	358	0.21	N.M.
Methotrexate		1.1	N.M.	292	0.06	N.M.
Oral immunosuppressants		5.6	1	314	21.47	10.1
Azathioprine		3.3	1	292	0.85	0.2
Teriflunomide		1.0	N.M.	347	52.36	4.5
Cladribine		1.2	N.M.	347	52.36	5.4
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		5.9	1	358	66.20	34.2
Natalizumab		4.1	1	358	76.74	27.6
Daclizumab		1.8	N.M.	358	41.84	6.5
Corticosteroids		37.3	9	7	11.95	0.5
Methylprednisolone		29.8	7	5	14.91	0.5
Other corticosteroids		7.6	2	14	0.29	N.M.
Oral immunomodulators		8.2	2	347	53.85	37.6
FTY-720		6.7	2	347	54.20	30.7
BG-12		0.8	N.M.	347	52.36	3.5
Laquinimod		0.8	N.M.	347	52.36	3.5
Spain	15					
Recombinant interferons		70.7	10	329	43.02	150.0
IFN-β-1b		20.4	3	329	38.09	37.1
IFN-β-1a (Avonex)		21.1	3	329	33.91	34.2
IFN-β-1a (Rebif)		29.1	4	329	53.05	73.7
Altered peptide ligands		11.6	2	333	35.03	19.6
Glatiramer acetate		9.6	1	329	34.82	16.0
MBP-8298		2.0	N.M.	358	36.11	3.7
Chemotherapeutics		2.7	N.M.	352	2.28	0.3
Mitoxantrone		1.5	N.M.	358	4.08	0.3
Cyclophosphamide		1.0	N.M.	358	0.17	N.M.
Methotrexate		0.2	N.M.	292	0.02	N.M.

(continued)

Table B-3 (cont.)

Assumptions Behind the 2015 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		5.8	1	320	24.76	7.2
Azathioprine		2.8	N.M.	292	0.52	0.1
Teriflunomide		1.0	N.M.	347	47.14	2.4
Cladribine		2.0	N.M.	347	47.14	4.7
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		5.0	1	358	62.14	16.3
Natalizumab		4.0	1	358	69.02	14.5
Daclizumab		1.0	N.M.	358	34.07	1.8
Corticosteroids		30.8	4	7	8.22	0.2
Methylprednisolone		23.5	3	5	10.68	0.2
Other corticosteroids		7.3	1	14	0.32	N.M.
Oral immunomodulators		8.1	1	347	48.20	19.6
FTY-720		6.6	1	347	48.45	16.0
BG-12		0.8	N.M.	347	47.14	1.8
Laquinimod		0.8	N.M.	347	47.14	1.8
United Kingdom	29					
Recombinant interferons		29.8	9	329	38.02	107.2
IFN-β-1b		4.0	1	329	28.56	10.7
IFN-β-1a (Avonex)		11.6	3	329	30.96	34.0
IFN-β-1a (Rebif)		14.2	4	329	46.43	62.5
Altered peptide ligands		12.3	4	332	30.82	36.3
Glatiramer acetate		10.7	3	329	29.39	29.7
MBP-8298		1.6	N.M.	358	40.50	6.6
Chemotherapeutics		2.4	1	352	1.16	0.3
Mitoxantrone		1.2	N.M.	358	2.09	0.3
Cyclophosphamide		1.0	N.M.	358	0.25	N.M.
Methotrexate		0.2	N.M.	292	0.08	N.M.
Oral immunosuppressants		3.0	1	329	31.80	9.5
Azathioprine		1.0	N.M.	292	1.13	0.1
Teriflunomide		1.0	N.M.	347	47.14	4.7
Cladribine		1.0	N.M.	347	47.14	4.7
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		5.2	2	358	63.07	34.0
Natalizumab		4.2	1	358	69.25	30.2
Daclizumab		1.0	N.M.	358	36.96	3.8
Corticosteroids		43.9	13	7	14.28	0.9
Methylprednisolone		34.8	10	5	17.89	0.9
Other corticosteroids		9.0	3	14	0.34	N.M.
Oral immunomodulators		6.0	2	347	47.92	28.9
FTY-720		4.4	1	347	48.20	21.3
BG-12		0.8	N.M.	347	47.14	3.8
Laquinimod		0.8	N.M.	347	47.14	3.8

(continued)

Table B-3 (cont.)

Assumptions Behind the 2015 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
Japan	4					
Recombinant interferons		72.0	3	329	40.46	42.4
IFN-β-1b		44.8	2	329	39.33	25.6
IFN-β-1a (Avonex)		27.2	1	329	42.33	16.7
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		2.6	N.M.	354	1.59	0.1
Mitoxantrone		1.3	N.M.	358	2.81	0.1
Cyclophosphamide		1.1	N.M.	358	0.38	N.M.
Methotrexate		0.1	N.M.	292	0.22	N.M.
Oral immunosuppressants		2.0	N.M.	292	2.95	0.1
Azathioprine		2.0	N.M.	292	2.95	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		4.4	N.M.	358	65.27	4.6
Natalizumab		4.4	N.M.	358	65.27	4.6
Daclizumab		—	—	—	—	—
Corticosteroids		53.6	2	7	21.39	0.2
Methylprednisolone		38.6	2	5	29.71	0.2
Other corticosteroids		15.0	1	14	—	—
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-4

Assumptions Behind the 2020 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
United States	233					
Recombinant interferons		50.0	116	329	37.71	1,437.5
IFN-β-1b		10.0	24	329	36.93	293.5
IFN-β-1a (Avonex)		22.0	51	329	29.43	495.0
IFN-β-1a (Rebif)		17.0	41	329	48.60	649.1
Altered peptide ligands		20.0	47	333	39.51	629.0
Glatiramer acetate		15.0	34	329	37.48	424.2
MBP-8298		5.0	13	358	45.00	204.7
Chemotherapeutics		4.0	10	354	2.58	8.8
Mitoxantrone		3.0	6	358	3.75	7.9
Cyclophosphamide		1.0	3	358	0.73	0.8
Methotrexate		—	1	292	0.24	N.M.
Oral immunosuppressants		7.0	17	326	37.62	214.5
Azathioprine		1.0	3	292	2.30	2.0
Teriflunomide		2.0	5	347	49.50	79.9
Cladribine		3.0	8	347	49.50	130.8
Mycophenolate mofetil		1.0	1	256	5.38	1.7
Monoclonal antibodies		10.0	22	358	48.64	482.8
Natalizumab		7.0	16	358	56.75	414.5
Daclizumab		3.0	7	358	29.06	68.3
Corticosteroids		36.0	83	7	6.75	2.8
Methylprednisolone		27.0	63	5	8.89	2.7
Other corticosteroids		9.0	20	14	0.10	N.M.
Oral immunomodulators		19.0	44	347	54.15	715.9
FTY-720		16.0	37	347	55.00	599.9
BG-12		1.0	3	347	49.50	58.0
Laquinimod		1.0	3	347	49.50	58.0
France	29					
Recombinant interferons		54.0	15	329	35.44	178.7
IFN-β-1b		8.0	2	329	36.16	27.8
IFN-β-1a (Avonex)		20.0	6	329	30.04	57.6
IFN-β-1a (Rebif)		25.0	7	329	39.61	93.3
Altered peptide ligands		15.0	4	332	33.79	47.5
Glatiramer acetate		11.0	3	329	33.08	34.5
MBP-8298		4.0	1	358	36.00	13.0
Chemotherapeutics		5.0	1	351	2.34	1.2
Mitoxantrone		3.0	1	358	3.28	1.1
Cyclophosphamide		1.0	N.M.	358	0.51	N.M.
Methotrexate		—	N.M.	292	0.09	N.M.

(continued)

Table B-4 (cont.)

Assumptions Behind the 2020 Multiple Sclerosis Market (All Populations)	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		11.0	3	299	25.06	26.1
Azathioprine		3.0	1	292	0.96	0.2
Teriflunomide		2.0	1	347	47.47	9.4
Cladribine		3.0	1	347	47.47	15.1
Mycophenolate mofetil		3.0	1	256	6.55	1.4
Monoclonal antibodies		7.0	2	358	62.40	44.8
Natalizumab		5.0	1	358	70.74	34.8
Daclizumab		2.0	1	358	44.03	10.0
Corticosteroids		35.0	10	7	17.06	0.8
Methylprednisolone		27.0	8	5	21.48	0.8
Other corticosteroids		7.0	2	14	0.47	N.M.
Oral immunomodulators		15.0	4	347	48.29	73.8
FTY-720		12.0	4	347	48.50	59.2
BG-12		2.0	N.M.	347	47.47	7.3
Laquinimod		2.0	N.M.	347	47.47	7.3
Germany	54					
Recombinant interferons		52.0	28	329	45.02	416.2
IFN-β-1b		11.0	6	329	43.18	85.7
IFN-β-1a (Avonex)		17.0	9	329	34.62	105.1
IFN-β-1a (Rebif)		24.0	13	329	53.36	225.3
Altered peptide ligands		16.0	8	332	36.00	102.0
Glatiramer acetate		12.0	6	329	35.47	74.8
MBP-8298		4.0	2	358	37.69	27.2
Chemotherapeutics		5.0	3	355	2.14	2.2
Mitoxantrone		4.0	2	358	2.73	2.1
Cyclophosphamide		1.0	1	358	0.28	N.M.
Methotrexate		—	N.M.	292	0.15	N.M.
Oral immunosuppressants		8.0	4	318	35.85	51.5
Azathioprine		2.0	1	292	2.19	0.9
Teriflunomide		2.0	1	347	51.84	19.3
Cladribine		3.0	2	347	51.84	31.3
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		7.0	4	358	64.79	85.7
Natalizumab		5.0	3	358	77.26	69.0
Daclizumab		2.0	1	358	38.55	16.6
Corticosteroids		44.0	24	7	13.24	1.5
Methylprednisolone		36.0	19	5	16.41	1.5
Other corticosteroids		9.0	5	14	0.28	N.M.
Oral immunomodulators		14.0	8	347	52.98	140.0
FTY-720		11.0	6	347	53.28	111.2
BG-12		1.0	1	347	51.84	14.4
Laquinimod		1.0	1	347	51.84	14.4

(continued)

Table B-4 (cont.)

Assumptions Behind the 2020 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Italy	25					
Recombinant interferons		55.0	14	329	37.89	172.4
IFN-β-1b		9.0	2	329	33.24	24.0
IFN-β-1a (Avonex)		18.0	4	329	27.18	40.0
IFN-β-1a (Rebif)		29.0	7	329	46.01	108.4
Altered peptide ligands		11.0	3	333	31.88	30.6
Glatiramer acetate		8.0	2	329	28.21	18.2
MBP-8298		3.0	1	358	40.28	12.4
Chemotherapeutics		4.0	1	344	1.04	0.4
Mitoxantrone		2.0	1	358	1.91	0.4
Cyclophosphamide		1.0	N.M.	358	0.21	N.M.
Methotrexate		1.0	N.M.	292	0.06	N.M.
Oral immunosuppressants		7.0	2	314	33.14	19.4
Azathioprine		3.0	1	292	0.83	0.1
Teriflunomide		2.0	1	347	52.36	9.1
Cladribine		2.0	1	347	52.36	10.2
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		8.0	2	358	68.46	45.9
Natalizumab		6.0	1	358	78.03	38.4
Daclizumab		2.0	1	358	41.84	7.5
Corticosteroids		37.0	9	7	11.78	0.5
Methylprednisolone		30.0	7	5	14.65	0.5
Other corticosteroids		8.0	2	14	0.29	N.M.
Oral immunomodulators		12.0	3	347	53.74	56.6
FTY-720		9.0	2	347	54.20	42.8
BG-12		2.0	N.M.	347	52.36	6.9
Laquinimod		2.0	N.M.	347	52.36	6.9
Spain	17					
Recombinant interferons		62.0	9	329	42.52	125.1
IFN-β-1b		16.0	2	329	38.39	29.0
IFN-β-1a (Avonex)		18.0	3	329	30.31	25.8
IFN-β-1a (Rebif)		28.0	4	329	53.19	73.7
Altered peptide ligands		12.0	2	333	33.40	19.2
Glatiramer acetate		9.0	1	329	32.00	13.3
MBP-8298		3.0	0	358	36.11	5.9
Chemotherapeutics		2.0	N.M.	352	1.15	0.2
Mitoxantrone		1.0	N.M.	358	2.17	0.2
Cyclophosphamide		1.0	N.M.	358	0.17	N.M.
Methotrexate		—	N.M.	292	0.02	N.M.

(continued)

Table B-4 (cont.)

Assumptions Behind the 2020 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		7.0	1	320	31.38	10.0
Azathioprine		3.0	N.M.	292	0.50	0.1
Teriflunomide		2.0	N.M.	347	47.14	4.7
Cladribine		2.0	N.M.	347	47.14	5.3
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		7.0	1	358	62.05	21.9
Natalizumab		6.0	1	358	70.25	19.7
Daclizumab		1.0	N.M.	358	34.07	2.2
Corticosteroids		31.0	5	7	8.17	0.2
Methylprednisolone		23.0	4	5	10.41	0.2
Other corticosteroids		7.0	1	14	0.31	N.M.
Oral immunomodulators		12.0	2	347	48.14	28.9
FTY-720		9.0	1	347	48.45	21.8
BG-12		2.0	N.M.	347	47.14	3.5
Laquinimod		2.0	N.M.	347	47.14	3.5
United Kingdom	32					
Recombinant interferons		33.0	11	329	36.73	128.3
IFN-β-1b		4.0	1	329	28.40	11.6
IFN-β-1a (Avonex)		13.0	4	329	27.69	37.1
IFN-β-1a (Rebif)		16.0	5	329	45.61	79.6
Altered peptide ligands		12.0	4	332	27.36	35.8
Glatiramer acetate		10.0	3	329	24.34	25.3
MBP-829B		2.0	1	358	40.50	10.5
Chemotherapeutics		2.0	1	352	1.05	0.3
Mitoxantrone		1.0	N.M.	358	2.05	0.2
Cyclophosphamide		1.0	N.M.	358	0.25	N.M.
Methotrexate		—	N.M.	292	0.08	N.M.
Oral immunosuppressants		5.0	2	329	37.94	21.3
Azathioprine		1.0	N.M.	292	1.13	0.1
Teriflunomide		2.0	1	347	47.14	10.6
Cladribine		2.0	1	347	47.14	10.6
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		7.0	2	358	64.51	51.7
Natalizumab		6.0	2	358	70.27	46.5
Daclizumab		1.0	N.M.	358	36.96	5.2
Corticosteroids		38.0	12	7	14.60	0.9
Methylprednisolone		31.0	10	5	17.60	0.9
Other corticosteroids		7.0	2	14	0.34	N.M.
Oral immunomodulators		9.0	3	347	47.84	50.3
FTY-720		6.0	2	347	48.20	33.5
BG-12		2.0	1	347	47.14	8.4
Laquinimod		2.0	1	347	47.14	8.4

(continued)

Table B-4 (cont.)

Assumptions Behind the 2020 Multiple Sclerosis Market (All Populations)

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Japan	5					
Recombinant interferons		71.0	3	329	34.23	38.8
IFN-β-1b		37.0	2	329	31.47	18.7
IFN-β-1a (Avonex)		34.0	2	329	37.25	20.1
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		2.0	N.M.	354	1.16	N.M.
Mitoxantrone		1.0	N.M.	358	2.05	N.M.
Cyclophosphamide		1.0	N.M.	358	0.28	N.M.
Methotrexate		—	N.M.	292	0.22	N.M.
Oral immunosuppressants		1.0	N.M.	292	2.23	N.M.
Azathioprine		1.0	N.M.	292	2.23	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		7.0	N.M.	358	65.27	7.9
Natalizumab		7.0	N.M.	358	65.27	7.9
Daclizumab		—	—	—	—	—
Corticosteroids		49.0	2	7	15.14	0.2
Methylprednisolone		35.0	2	5	20.75	0.2
Other corticosteroids		13.0	1	14	—	—
Oral immunomodulators		1.0	N.M.	—	62.43	1.0
FTY-720		1.0	N.M.	—	62.43	1.0
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-5

Assumptions Behind the 2005 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
United States	147					
Recombinant interferons		73.0	107	329	38.49	1,356.1
IFN-β-1b		9.0	13	329	34.51	149.9
IFN-β-1a (Avonex)		47.0	69	329	36.90	837.0
IFN-β-1a (Rebif)		17.0	25	329	45.00	369.2
Altered peptide ligands		42.0	62	329	37.71	764.4
Glatiramer acetate		42.0	62	329	37.71	764.4
MBP-8298		—	—	—	—	—
Chemotherapeutics		4.5	7	350	7.78	18.4
Mitoxantrone		2.5	4	358	13.52	17.8
Cyclophosphamide		1.5	2	358	0.74	0.6
Methotrexate		0.5	1	292	0.24	0.1
Oral immunosuppressants		2.0	3	292	2.30	2.0
Azathioprine		2.0	3	292	2.30	2.0
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		0.7	1	358	56.75	20.9
Natalizumab		0.7	1	358	56.75	20.9
Daclizumab		—	—	—	—	—
Corticosteroids		40.0	59	8	6.25	1.8
Methylprednisolone		28.0	41	5	8.89	1.8
Other corticosteroids		12.0	18	14	0.10	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
France	20					
Recombinant interferons		75.0	15	329	37.74	185.9
IFN-β-1b		11.0	2	329	37.47	27.1
IFN-β-1a (Avonex)		41.0	8	329	37.55	101.1
IFN-β-1a (Rebif)		23.0	5	329	38.22	57.7
Altered peptide ligands		14.0	3	329	35.96	33.1
Glatiramer acetate		14.0	3	329	35.96	33.1
MBP-8298		—	—	—	—	—
Chemotherapeutics		5.0	1	331	1.70	0.6
Mitoxantrone		2.0	N.M.	358	3.86	0.6
Cyclophosphamide		1.0	N.M.	358	0.56	N.M.
Methotrexate		2.0	N.M.	292	0.10	N.M.

(continued)

Table B-5 (cont.)

Assumptions Behind the 2005 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		6.0	1	286	3.05	1.0
Azathioprine		5.0	1	292	1.09	0.3
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		1.0	N.M.	256	12.84	0.7
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		36.0	7	7	18.94	0.7
Methylprednisolone		28.0	6	5	24.20	0.7
Other corticosteroids		8.0	2	14	0.54	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Germany	35					
Recombinant interferons		77.0	27	329	47.33	419.6
IFN-β-1b		25.0	9	329	43.40	124.9
IFN-β-1a (Avonex)		24.0	8	329	43.27	119.6
IFN-β-1a (Rebif)		28.0	10	329	54.32	175.1
Altered peptide ligands		24.0	8	329	40.82	112.8
Glatiramer acetate		24.0	8	329	40.82	112.8
MBP-8298		—	—	—	—	—
Chemotherapeutics		6.0	2	347	1.98	1.5
Mitoxantrone		3.0	1	358	3.60	1.4
Cyclophosphamide		2.0	1	358	0.45	0.1
Methotrexate		1.0	N.M.	292	0.16	N.M.
Oral immunosuppressants		6.0	2	292	2.20	1.4
Azathioprine		6.0	2	292	2.20	1.4
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		45.0	16	7	21.35	1.7
Methylprednisolone		35.0	12	5	27.35	1.6
Other corticosteroids		10.0	4	14	0.36	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-5 (cont.)

Assumptions Behind the 2005 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Italy	18					
Recombinant interferons		69.0	13	329	39.19	162.2
IFN-β-1b		12.0	2	329	34.38	24.7
IFN-β-1a (Avonex)		25.0	5	329	33.98	51.0
IFN-β-1a (Rebif)		32.0	6	329	45.07	86.5
Altered peptide ligands		11.0	2	329	31.12	20.5
Glatiramer acetate		11.0	2	329	31.12	20.5
MBP-8298		—	—	—	—	—
Chemotherapeutics		7.0	1	330	0.91	0.4
Mitoxantrone		3.0	1	358	1.98	0.4
Cyclophosphamide		1.0	N.M.	358	0.23	N.M.
Methotrexate		3.0	1	292	0.06	N.M.
Oral immunosuppressants		6.0	1	292	0.89	0.3
Azathioprine		6.0	1	292	0.89	0.3
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		36.0	7	7	12.29	0.4
Methylprednisolone		28.0	5	5	15.65	0.4
Other corticosteroids		8.0	1	14	0.52	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Spain	10					
Recombinant interferons		87.0	9	329	43.23	126.7
IFN-β-1b		29.0	3	329	38.58	37.7
IFN-β-1a (Avonex)		27.0	3	329	37.88	34.5
IFN-β-1a (Rebif)		31.0	3	329	52.23	54.6
Altered peptide ligands		9.0	1	329	35.30	10.7
Glatiramer acetate		9.0	1	329	35.30	10.7
MBP-8298		—	—	—	—	—
Chemotherapeutics		2.5	N.M.	331	0.64	0.1
Mitoxantrone		0.5	N.M.	358	2.77	0.1
Cyclophosphamide		1.0	N.M.	358	0.19	N.M.
Methotrexate		1.0	N.M.	292	0.02	N.M.

(continued)

Table B-5 (cont.)

Assumptions Behind the 2005 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		4.0	N.M.	292	0.57	0.1
Azathioprine		4.0	N.M.	292	0.57	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		31.0	3	7	8.50	0.1
Methylprednisolone		23.0	2	5	11.33	0.1
Other corticosteroids		8.0	1	14	0.35	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
United Kingdom	10					
Recombinant interferons		18.0	2	329	40.93	23.6
IFN-β-1b		5.0	N.M.	329	31.69	5.1
IFN-β-1a (Avonex)		5.0	N.M.	329	37.95	6.1
IFN-β-1a (Rebif)		8.0	1	329	48.56	12.4
Altered peptide ligands		13.0	1	329	30.99	12.9
Glatiramer acetate		13.0	1	329	30.99	12.9
MBP-8298		—	—	—	—	—
Chemotherapeutics		4.0	N.M.	341	1.22	0.2
Mitoxantrone		2.0	N.M.	358	2.22	0.2
Cyclophosphamide		1.0	N.M.	358	0.37	N.M.
Methotrexate		1.0	N.M.	292	0.08	N.M.
Oral immunosuppressants		1.0	N.M.	292	1.35	N.M.
Azathioprine		1.0	N.M.	292	1.35	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		60.0	6	8	12.99	0.4
Methylprednisolone		40.0	4	5	19.34	0.4
Other corticosteroids		20.0	2	14	0.30	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-5 (cont.)

Assumptions Behind the 2005 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Japan	3					
Recombinant interferons		76.0	2	329	42.75	32.4
IFN-β-1b		76.0	2	329	42.75	32.4
IFN-β-1a (Avonex)		—	—	—	—	—
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		4.0	N.M.	341	2.17	0.1
Mitoxantrone		2.0	N.M.	358	3.95	0.1
Cyclophosphamide		1.0	N.M.	358	0.54	N.M.
Methotrexate		1.0	N.M.	292	0.23	N.M.
Oral immunosuppressants		4.0	N.M.	292	4.21	0.1
Azathioprine		4.0	N.M.	292	4.21	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		64.0	2	8	30.52	0.3
Methylprednisolone		44.0	1	5	44.39	0.3
Other corticosteroids		20.0	1	14	—	—
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-6

Assumptions Behind the 2010 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
United States	155					
Recombinant interferons		67.0	104	329	39.64	1,354.4
IFN-β-1b		6.0	9	329	35.03	107.2
IFN-β-1a (Avonex)		43.0	67	329	36.90	809.2
IFN-β-1a (Rebif)		18.0	28	329	47.71	438.0
Altered peptide ligands		38.0	59	329	38.28	741.8
Glatiramer acetate		38.0	59	329	38.28	741.8
MBP-8298		—	—	—	—	—
Chemotherapeutics		3.0	5	358	6.73	11.2
Mitoxantrone		2.0	3	358	9.73	10.8
Cyclophosphamide		1.0	2	358	0.73	0.4
Methotrexate		—	—	—	—	—
Oral immunosuppressants		2.0	3	319	25.90	27.7
Azathioprine		1.0	2	292	2.30	1.0
Teriflunomide		—	—	—	—	—
Cladribine		1.0	2	347	49.50	26.6
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		7.0	11	358	61.00	237.1
Natalizumab		5.0	8	358	73.77	204.8
Daclizumab		2.0	3	358	29.06	32.3
Corticosteroids		39.0	61	7	6.41	1.9
Methylprednisolone		28.0	43	5	8.89	1.9
Other corticosteroids		11.0	17	14	0.10	N.M.
Oral immunomodulators		2.0	3	347	55.00	59.2
FTY-720		2.0	3	347	55.00	59.2
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
France	21					
Recombinant interferons		73.0	15	329	37.19	186.0
IFN-β-1b		8.0	2	329	36.24	19.9
IFN-β-1a (Avonex)		40.0	8	329	36.05	98.8
IFN-β-1a (Rebif)		25.0	5	329	39.33	67.3
Altered peptide ligands		20.0	4	329	36.14	49.5
Glatiramer acetate		20.0	4	329	36.14	49.5
MBP-8298		—	—	—	—	—
Chemotherapeutics		4.0	1	341	2.03	0.6
Mitoxantrone		2.0	N.M.	358	3.75	0.6
Cyclophosphamide		1.0	N.M.	358	0.54	N.M.
Methotrexate		1.0	N.M.	292	0.09	N.M.

(continued)

Table B-6 (cont.)

Assumptions Behind the 2010 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/Day ($)	Sales ($MM)
Oral immunosuppressants		7.0	1	295	9.37	4.4
Azathioprine		5.0	1	292	1.05	0.3
Teriflunomide		—	—	—	—	—
Cladribine		1.0	N.M.	347	47.47	3.4
Mycophenolate mofetil		1.0	N.M.	256	12.84	0.7
Monoclonal antibodies		4.0	1	358	70.74	21.1
Natalizumab		4.0	1	358	70.74	21.1
Daclizumab		—	—	—	—	—
Corticosteroids		36.0	8	7	17.53	0.7
Methylprednisolone		28.0	6	5	22.39	0.6
Other corticosteroids		8.0	2	14	0.51	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
8G-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Germany	37					
Recombinant interferons		76.0	28	329	47.02	432.8
IFN-β-1b		21.0	8	329	41.55	105.7
IFN-β-1a (Avonex)		25.0	9	329	41.11	124.5
IFN-β-1a (Rebif)		30.0	11	329	55.77	202.6
Altered peptide ligands		21.0	8	329	41.02	104.3
Glatiramer acetate		21.0	8	329	41.02	104.3
MBP-8298		—	—	—	—	—
Chemotherapeutics		4.0	1	358	1.80	0.9
Mitoxantrone		2.0	1	358	3.23	0.9
Cyclophosphamide		2.0	1	358	0.36	0.1
Methotrexate		—	—	—	—	—
Oral immunosuppressants		6.0	2	301	10.47	7.8
Azathioprine		5.0	2	292	2.19	1.2
Teriflunomide		—	—	—	—	—
Cladribine		1.0	N.M.	347	51.84	6.6
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		4.0	1	358	77.26	40.8
Natalizumab		4.0	1	358	77.26	40.8
Daclizumab		—	—	—	—	—
Corticosteroids		45.0	17	7	14.97	1.2
Methylprednisolone		35.0	13	5	19.15	1.2
Other corticosteroids		10.0	4	14	0.34	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-6 (cont.)

Assumptions Behind the 2010 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/Day ($)	Sales ($MM)
Italy	19					
Recombinant interferons		69.0	13	329	39.13	167.0
IFN-β-1b		9.0	2	329	33.25	18.5
IFN-β-1a (Avonex)		27.0	5	329	32.62	54.5
IFN-β-1a (Rebif)		33.0	6	329	46.05	94.0
Altered peptide ligands		14.0	3	329	31.27	27.1
Glatiramer acetate		14.0	3	329	31.27	27.1
MBP-8298		—	—	—	—	—
Chemotherapeutics		4.0	1	341	1.04	0.3
Mitoxantrone		2.0	N.M.	358	1.94	0.3
Cyclophosphamide		1.0	N.M.	358	0.22	N.M.
Methotrexate		1.0	N.M.	292	0.06	N.M.
Oral immunosuppressants		6.0	1	301	9.45	3.7
Azathioprine		5.0	1	292	0.87	0.2
Teriflunomide		—	—	—	—	—
Cladribine		1.0	N.M.	347	52.36	3.4
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		3.0	1	358	78.03	15.8
Natalizumab		3.0	1	358	78.03	15.8
Daclizumab		—	—	—	—	—
Corticosteroids		36.0	7	7	12.07	0.4
Methylprednisolone		28.0	5	5	15.44	0.4
Other corticosteroids		8.0	2	14	0.29	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Spain	11					
Recombinant interferons		85.0	9	329	43.03	127.4
IFN-β-1b		25.0	3	329	37.31	32.5
IFN-β-1a (Avonex)		28.0	3	329	36.37	35.5
IFN-β-1a (Rebif)		32.0	3	329	53.32	59.4
Altered peptide ligands		12.0	1	329	35.48	14.8
Glatiramer acetate		12.0	1	329	35.48	14.8
MBP-8298		—	—	—	—	—
Chemotherapeutics		2.0	N.M.	358	1.36	0.1
Mitoxantrone		1.0	N.M.	358	2.55	0.1
Cyclophosphamide		1.0	N.M.	358	0.17	N.M.
Methotrexate		—	—	—	—	—

(continued)

Table B-6 (cont.)

Assumptions Behind the 2010 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/Day ($)	Sales ($MM)
Oral immunosuppressants		4.0	N.M.	306	12.19	1.7
Azathioprine		3.0	N.M.	292	0.54	0.1
Teriflunomide		—	—	—	—	—
Cladribine		1.0	N.M.	347	47.14	1.8
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		3.0	N.M.	358	70.25	8.0
Natalizumab		3.0	N.M.	358	70.25	8.0
Daclizumab		—	—	—	—	—
Corticosteroids		31.0	3	7	8.22	0.1
Methylprednisolone		23.0	2	5	10.97	0.1
Other corticosteroids		8.0	1	14	0.33	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
United Kingdom	18					
Recombinant interferons		25.0	4	329	39.24	56.9
IFN-β-1b		5.0	1	329	29.44	8.5
IFN-β-1a (Avonex)		9.0	2	329	34.91	18.2
IFN-β-1a (Rebif)		11.0	2	329	47.24	30.2
Altered peptide ligands		15.0	3	329	29.97	26.1
Glatiramer acetate		15.0	3	329	29.97	26.1
MBP-B298		—	—	—	—	—
Chemotherapeutics		2.5	N.M.	345	0.97	0.2
Mitoxantrone		1.0	N.M.	358	2.12	0.1
Cyclophosphamide		1.0	N.M.	358	0.26	N.M.
Methotrexate		0.5	N.M.	292	0.08	N.M.
Oral immunosuppressants		1.0	N.M.	292	1.13	0.1
Azathioprine		1.0	N.M.	292	1.13	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		3.0	1	358	70.26	13.3
Natalizumab		3.0	1	358	70.26	13.3
Daclizumab		—	—	—	—	—
Corticosteroids		50.0	9	8	12.82	0.6
Methylprednisolone		35.0	6	5	18.18	0.6
Other corticosteroids		15.0	3	14	0.32	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-6 (cont.)

Assumptions Behind the 2010 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
Japan	3					
Recombinant interferons		75.0	3	329	43.27	36.4
IFN-β-1b		63.0	2	329	42.75	30.2
IFN-β-1a (Avonex)		12.0	N.M.	329	46.01	6.2
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		3.0	N.M.	336	1.30	N.M.
Mitoxantrone		1.0	N.M.	358	3.23	N.M.
Cyclophosphamide		1.0	N.M.	358	0.44	N.M.
Methotrexate		1.0	N.M.	292	0.22	N.M.
Oral immunosuppressants		3.0	N.M.	292	3.43	0.1
Azathioprine		3.0	N.M.	292	3.43	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		59.0	2	7	24.94	0.2
Methylprednisolone		42.0	1	5	35.03	0.2
Other corticosteroids		17.0	1	14	—	—
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-7

Assumptions Behind the 2015 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
United States	165					
Recombinant interferons		51.0	84	329	38.85	1,071.3
IFN-β-1b		4.0	7	329	36.61	79.2
IFN-β-1a (Avonex)		30.0	49	329	34.13	553.6
IFN-β-1a (Rebif)		17.0	28	329	47.71	438.5
Altered peptide ligands		25.0	41	330	40.01	542.9
Glatiramer acetate		24.0	40	329	39.80	516.4
MBP-8298		1.0	2	358	45.00	26.5
Chemotherapeutics		3.0	5	358	4.21	7.4
Mitoxantrone		2.0	3	358	5.95	7.0
Cyclophosphamide		1.0	2	358	0.73	0.4
Methotrexate		—	—	—	—	—
Oral immunosuppressants		5.0	8	336	40.06	114.1
Azathioprine		1.0	2	292	2.30	1.1
Teriflunomide		1.0	2	347	49.50	28.2
Cladribine		3.0	5	347	49.50	84.7
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		9.0	15	358	63.83	338.2
Natalizumab		7.0	12	358	73.77	304.0
Daclizumab		2.0	3	358	29.06	34.2
Corticosteroids		38.0	63	7	6.58	2.0
Methylprednisolone		28.0	46	5	8.89	2.0
Other corticosteroids		10.0	16	14	0.10	N.M.
Oral immunomodulators		17.0	28	347	54.35	527.3
FTY-720		15.0	25	347	55.00	470.8
BG-12		1.0	2	347	49.50	28.2
Laquinimod		1.0	2	347	49.50	28.2
France	22					
Recombinant interferons		60.0	13	329	36.33	156.4
IFN-β-1b		5.0	1	329	36.61	13.1
IFN-β-1a (Avonex)		29.0	6	329	33.61	69.9
IFN-β-1a (Rebif)		26.0	6	329	39.31	73.3
Altered peptide ligands		18.0	4	330	36.60	47.5
Glatiramer acetate		17.0	4	329	36.64	44.7
MBP-8298		1.0	N.M.	358	36.00	2.8
Chemotherapeutics		3.0	1	358	2.59	0.6
Mitoxantrone		2.0	N.M.	358	3.63	0.6
Cyclophosphamide		1.0	N.M.	358	0.52	N.M.
Methotrexate		—	—	—	—	—

(continued)

Table B-7 (cont.)

Assumptions Behind the 2015 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		8.0	2	308	19.50	11.6
Azathioprine		4.0	1	292	1.00	0.3
Teriflunomide		1.0	N.M.	347	47.47	3.6
Cladribine		2.0	N.M.	347	47.47	7.2
Mycophenolate mofetil		1.0	N.M.	256	9.63	0.5
Monoclonal antibodies		7.0	2	358	63.11	34.5
Natalizumab		5.0	1	358	70.74	27.6
Daclizumab		2.0	N.M.	358	44.03	6.9
Corticosteroids		36.0	8	7	17.28	0.7
Methylprednisolone		28.0	6	5	22.08	0.7
Other corticosteroids		8.0	2	14	0.48	N.M.
Oral immunomodulators		13.0	3	347	48.34	47.6
FTY-720		11.0	2	347	48.50	40.4
BG-12		1.0	N.M.	347	47.47	3.6
Laquinimod		1.0	N.M.	347	47.47	3.6
Germany	**40**					
Recombinant interferons		61.0	24	329	46.04	365.8
IFN-β-1b		13.0	5	329	41.77	70.7
IFN-β-1a (Avonex)		20.0	8	329	36.78	95.8
IFN-β-1a (Rebif)		28.0	11	329	54.64	199.2
Altered peptide ligands		19.0	8	330	40.48	100.6
Glatiramer acetate		18.0	7	329	40.64	95.3
MBP-8298		1.0	N.M.	358	37.69	5.3
Chemotherapeutics		3.0	1	358	1.21	0.5
Mitoxantrone		1.0	N.M.	358	2.98	0.4
Cyclophosphamide		2.0	1	358	0.32	0.1
Methotrexate		—	—	—	—	—
Oral immunosuppressants		7.0	3	315	23.47	22.4
Azathioprine		4.0	2	292	2.19	1.0
Teriflunomide		1.0	N.M.	347	51.84	7.1
Cladribine		2.0	1	347	51.84	14.3
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		7.0	3	358	66.20	65.7
Natalizumab		5.0	2	358	77.26	54.8
Daclizumab		2.0	1	358	38.55	10.9
Corticosteroids		45.0	18	7	13.90	1.2
Methylprednisolone		35.0	14	5	17.78	1.2
Other corticosteroids		10.0	4	14	0.31	N.M.
Oral immunomodulators		12.0	5	347	53.04	87.5
FTY-720		10.0	4	347	53.28	73.2
BG-12		1.0	N.M.	347	51.84	7.1
Laquinimod		1.0	N.M.	347	51.84	7.1

(continued)

Table B-7 (cont.)

Assumptions Behind the 2015 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Italy	19					
Recombinant interferons		63.0	12	329	39.02	153.8
IFN-β-1b		6.0	1	329	33.28	12.5
IFN-β-1a (Avonex)		23.0	4	329	30.41	43.8
IFN-β-1a (Rebif)		34.0	6	329	45.85	97.6
Altered peptide ligands		13.0	2	331	31.43	25.8
Glatiramer acetate		12.0	2	329	30.69	23.0
MBP-8298		1.0	N.M.	358	40.28	2.7
Chemotherapeutics		2.0	N.M.	358	1.07	0.1
Mitoxantrone		1.0	N.M.	358	1.93	0.1
Cyclophosphamide		1.0	N.M.	358	0.21	N.M.
Methotrexate		—	—	—	—	—
Oral immunosuppressants		6.0	1	310	18.02	7.1
Azathioprine		4.0	1	292	0.85	0.2
Teriflunomide		1.0	N.M.	347	52.36	3.5
Cladribine		1.0	N.M.	347	52.36	3.5
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		7.0	1	358	67.69	32.3
Natalizumab		5.0	1	358	78.03	26.6
Daclizumab		2.0	N.M.	358	41.84	5.7
Corticosteroids		36.0	7	7	11.66	0.4
Methylprednisolone		28.0	5	5	14.91	0.4
Other corticosteroids		8.0	2	14	0.29	N.M.
Oral immunomodulators		10.0	2	347	53.83	35.6
FTY-720		8.0	2	347	54.20	28.6
BG-12		1.0	N.M.	347	52.36	3.5
Laquinimod		1.0	N.M.	347	52.36	3.5
Spain	11					
Recombinant interferons		70.0	8	329	43.50	110.6
IFN-β-1b		14.0	2	329	38.09	19.4
IFN-β-1a (Avonex)		24.0	3	329	33.91	29.6
IFN-β-1a (Rebif)		32.0	4	329	53.05	61.7
Altered peptide ligands		13.0	2	331	34.92	16.6
Glatiramer acetate		12.0	1	329	34.82	15.2
MBP-8298		1.0	N.M.	358	36.11	1.4
Chemotherapeutics		2.0	N.M.	358	1.28	0.1
Mitoxantrone		1.0	N.M.	358	2.39	0.1
Cyclophosphamide		1.0	N.M.	358	0.17	N.M.
Methotrexate		—	—	—	—	—

(continued)

Table B-7 (cont.)

Assumptions Behind the 2015 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		6.0	1	319	23.83	5.5
Azathioprine		3.0	N.M.	292	0.52	0.1
Teriflunomide		1.0	N.M.	347	47.14	1.8
Cladribine		2.0	N.M.	347	47.14	3.6
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		6.0	1	358	64.22	15.2
Natalizumab		5.0	1	358	70.25	13.9
Daclizumab		1.0	N.M.	358	34.07	1.4
Corticosteroids		31.0	4	7	8.01	0.1
Methylprednisolone		23.0	3	5	10.68	0.1
Other corticosteroids		8.0	1	14	0.32	N.M.
Oral immunomodulators		10.0	1	347	48.19	18.5
FTY-720		8.0	1	347	48.45	14.9
8G-12		1.0	N.M.	347	47.14	1.8
Laquinimod		1.0	N.M.	347	47.14	1.8
United Kingdom	23					
Recombinant interferons		30.0	7	329	38.45	88.1
IFN-β-1b		3.0	1	329	28.56	6.5
IFN-β-1a (Avonex)		12.0	3	329	30.96	28.4
IFN-β-1a (Rebif)		15.0	3	329	46.43	53.2
Altered peptide ligands		14.0	3	331	30.18	32.5
Glatiramer acetate		13.0	3	329	29.39	29.2
MBP-8298		1.0	N.M.	358	40.50	3.4
Chemotherapeutics		2.0	N.M.	358	1.17	0.2
Mitoxantrone		1.0	N.M.	358	2.09	0.2
Cyclophosphamide		1.0	N.M.	358	0.25	N.M.
Methotrexate		—	—	—	—	—
Oral immunosuppressants		3.0	1	329	31.80	7.7
Azathioprine		1.0	N.M.	292	1.13	0.1
Teriflunomide		1.0	N.M.	347	47.14	3.8
Cladribine		1.0	N.M.	347	47.14	3.8
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		6.0	1	358	64.71	32.3
Natalizumab		5.0	1	358	70.26	29.2
Daclizumab		1.0	N.M.	358	36.96	3.1
Corticosteroids		40.0	9	7	13.50	0.6
Methylprednisolone		30.0	7	5	17.89	0.6
Other corticosteroids		10.0	2	14	0.34	N.M.
Oral immunomodulators		7.0	2	347	47.90	27.0
FTY-720		5.0	1	347	48.20	19.4
BG-12		1.0	N.M.	347	47.14	3.8
Laquinimod		1.0	N.M.	347	47.14	3.8

(continued)

Table B-7 (cont.)

Assumptions Behind the 2015 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Japan	4					
Recombinant interferons		74.0	3	329	40.55	37.4
IFN-β-1b		44.0	2	329	39.33	21.6
IFN-β-1a (Avonex)		30.0	1	329	42.33	15.8
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		2.0	N.M.	358	1.60	N.M.
Mitoxantrone		1.0	N.M.	358	2.81	N.M.
Cyclophosphamide		1.0	N.M.	358	0.38	N.M.
Methotrexate		—	—	—	—	—
Oral immunosuppressants		2.0	N.M.	292	2.95	0.1
Azathioprine		2.0	N.M.	292	2.95	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		5.0	N.M.	358	65.27	4.4
Natalizumab		5.0	N.M.	358	65.27	4.4
Daclizumab		—	—	—	—	—
Corticosteroids		55.0	2	7	21.61	0.2
Methylprednisolone		40.0	2	5	29.71	0.2
Other corticosteroids		15.0	1	14	—	—
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-8

Assumptions Behind the 2020 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
United States	169					
Recombinant interferons		43.0	73	329	36.64	875.1
IFN-β-1b		3.0	5	329	36.93	61.5
IFN-β-1a (Avonex)		25.0	42	329	29.43	408.7
IFN-β-1a (Rebif)		15.0	25	329	48.60	404.9
Altered peptide ligands		23.0	39	330	39.34	498.0
Glatiramer acetate		20.0	34	329	37.48	416.4
MBP-8298		3.0	5	358	45.00	81.7
Chemotherapeutics		3.0	5	358	2.74	5.0
Mitoxantrone		2.0	3	358	3.75	4.5
Cyclophosphamide		1.0	2	358	0.73	0.4
Methotrexate			—	—	—	—
Oral immunosuppressants		6.0	10	336	41.63	146.2
Azathioprine		1.0	2	292	2.30	1.1
Teriflunomide		2.0	3	347	49.50	58.0
Cladribine		3.0	5	347	49.50	87.1
Mycophenolate mofetil			—	—	—	—
Monoclonal antibodies		11.0	19	358	65.64	436.7
Natalizumab		9.0	15	358	73.77	401.6
Daclizumab		2.0	3	358	29.06	35.2
Corticosteroids		37.0	63	7	6.76	2.1
Methylprednisolone		28.0	47	5	8.89	2.1
Other corticosteroids		9.0	15	14	0.10	N.M.
Oral immunomodulators		24.0	41	347	54.08	664.3
FTY-720		20.0	34	347	55.00	548.2
BG-12		2.0	3	347	49.50	58.0
Laquinimod		2.0	3	347	49.50	58.0
France	29					
Recombinant interferons		54.0	12	329	35.10	138.3
IFN-β-1b		4.0	1	329	36.16	10.6
IFN-β-1a (Avonex)		24.0	5	329	30.04	52.6
IFN-β-1a (Rebif)		15.0	6	329	39.61	75.1
Altered peptide ligands		23.0	4	330	34.09	39.5
Glatiramer acetate		20.0	3	329	33.08	33.8
MBP-8298		3.0	N.M.	358	36.00	5.7
Chemotherapeutics		3.0	1	358	2.36	0.6
Mitoxantrone		2.0	N.M.	358	3.28	0.5
Cyclophosphamide		1.0	N.M.	358	0.51	N.M.
Methotrexate		—	—	—	—	—

(continued)

Table B-8 (cont.)

Assumptions Behind the 2020 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		6.0	2	308	27.42	18.8
Azathioprine		1.0	1	292	0.96	0.2
Teriflunomide		2.0	N.M.	347	47.47	7.3
Cladribine		3.0	1	347	47.47	11.0
Mycophenolate mofetil		1.0	N.M.	256	6.55	0.4
Monoclonal antibodies		11.0	2	358	64.06	40.7
Natalizumab		9.0	1	358	70.74	33.7
Daclizumab		2.0	N.M.	358	44.03	7.0
Corticosteroids		37.0	8	7	16.84	0.7
Methylprednisolone		28.0	6	5	21.48	0.7
Other corticosteroids		9.0	2	14	0.47	N.M.
Oral immunomodulators		24.0	4	347	48.28	70.7
FTY-720		20.0	3	347	48.50	56.0
BG-12		2.0	N.M.	347	47.47	7.3
Laquinimod		2.0	N.M.	347	47.47	7.3
Germany	40					
Recombinant interferons		53.0	21	329	45.27	315.9
IFN-β-1b		9.0	4	329	43.18	51.2
IFN-β-1a (Avonex)		18.0	7	329	34.62	82.1
IFN-β-1a (Rebif)		26.0	10	329	53.36	182.7
Altered peptide ligands		17.0	7	330	36.32	80.9
Glatiramer acetate		15.0	6	329	35.47	70.1
MBP-8298		2.0	1	358	37.69	10.8
Chemotherapeutics		2.0	1	358	1.51	0.4
Mitoxantrone		1.0	N.M.	358	2.73	0.4
Cyclophosphamide		1.0	N.M.	358	0.28	N.M.
Methotrexate		—	—	—	—	—
Oral immunosuppressants		8.0	3	315	33.22	36.8
Azathioprine		3.0	1	292	2.19	0.8
Teriflunomide		2.0	1	347	51.84	14.4
Cladribine		3.0	1	347	51.84	21.6
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		8.0	3	358	67.58	77.5
Natalizumab		6.0	2	358	77.26	66.5
Daclizumab		2.0	1	358	38.55	11.1
Corticosteroids		45.0	18	7	12.84	1.1
Methylprednisolone		35.0	14	5	16.41	1.1
Other corticosteroids		10.0	4	14	0.28	N.M.
Oral immunomodulators		18.0	7	347	52.96	132.5
FTY-720		14.0	6	347	53.28	103.7
BG-12		2.0	1	347	51.84	14.4
Laquinimod		2.0	1	347	51.84	14.4

(continued)

Table B-8 (cont.)

Assumptions Behind the 2020 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
Italy	19					
Recombinant interferons		57.0	11	329	38.18	136.2
IFN-β-1b		4.0	1	329	33.24	8.3
IFN-β-1a (Avonex)		21.0	4	329	27.18	35.7
IFN-β-1a (Rebif)		32.0	6	329	46.01	92.1
Altered peptide ligands		12.0	2	331	31.56	23.1
Glatiramer acetate		10.0	2	329	28.21	17.7
MBP-8298		2.0	N.M.	358	40.2B	5.5
Chemotherapeutics		2.0	N.M.	358	1.06	0.1
Mitoxantrone		1.0	N.M.	358	1.91	0.1
Cyclophosphamide		1.0	N.M.	358	0.21	N.M.
Methotrexate		—	—	—	—	—
Oral immunosuppressants		7.0	1	310	30.28	14.0
Azathioprine		3.0	1	292	0.83	0.1
Teriflunomide		2.0	N.M.	347	52.36	6.9
Cladribine		2.0	N.M.	347	52.36	6.9
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		9.0	2	358	69.99	42.9
Natalizumab		7.0	1	358	78.03	37.2
Daclizumab		2.0	N.M.	358	41.84	5.7
Corticosteroids		36.0	7	7	11.48	0.4
Methylprednisolone		28.0	5	5	14.65	0.4
Other corticosteroids		8.0	2	14	0.29	N.M.
Oral immunomodulators		15.0	3	347	53.71	53.2
FTY-720		11.0	2	347	54.20	39.4
BG-12		2.0	N.M.	347	52.36	6.9
Laquinimod		2.0	N.M.	347	52.36	6.9
Spain	11					
Recombinant interferons		60.0	7	329	43.10	92.2
IFN-β-1b		10.0	1	329	38.39	13.7
IFN-β-1a (Avonex)		20.0	2	329	30.31	21.6
IFN-β-1a (Rebif)		30.0	3	329	53.19	56.9
Altered peptide ligands		13.0	1	331	33.64	15.4
Glatiramer acetate		11.0	1	329	32.00	12.6
MBP-8298		2.0	N.M.	358	36.11	2.8
Chemotherapeutics		2.0	N.M.	358	1.17	0.1
Mitoxantrone		1.0	N.M.	358	2.17	0.1
Cyclophosphamide		1.0	N.M.	358	0.17	N.M.
Methotrexate		—	—	—	—	—

(continued)

Table B-8 (cont.)

Assumptions Behind the 2020 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		7.0	1	319	27.15	7.1
Azathioprine		3.0	N.M.	292	0.50	N.M.
Teriflunomide		2.0	N.M.	347	47.14	3.5
Cladribine		2.0	N.M.	347	47.14	3.6
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		8.0	1	358	65.73	20.4
Natalizumab		7.0	1	358	70.25	19.1
Daclizumab		1.0	N.M.	358	34.07	1.3
Corticosteroids		31.0	3	7	7.83	0.1
Methylprednisolone		23.0	2	5	10.41	0.1
Other corticosteroids		8.0	1	14	0.31	N.M.
Oral immunomodulators		15.0	2	347	48.10	27.1
FTY-720		11.0	1	347	48.45	20.0
BG-12		2.0	N.M.	347	47.14	3.5
Laquinimod		2.0	N.M.	347	47.14	3.5
United Kingdom	26					
Recombinant interferons		33.0	9	329	36.99	103.3
IFN-β-1b		3.0	1	329	28.40	7.2
IFN-β-1a (Avonex)		13.0	3	329	27.69	30.5
IFN-β-1a (Rebif)		17.0	4	329	45.61	65.6
Altered peptide ligands		13.0	3	331	25.84	28.5
Glatiramer acetate		12.0	3	329	24.34	24.7
MBP-8298		1.0	N.M.	358	40.50	3.7
Chemotherapeutics		2.0	1	358	1.15	0.2
Mitoxantrone		1.0	N.M.	358	2.05	0.2
Cyclophosphamide		1.0	N.M.	358	0.25	N.M.
Methotrexate		—	—	—	—	—
Oral immunosuppressants		5.0	1	329	37.94	16.9
Azathioprine		1.0	N.M.	292	1.13	0.1
Teriflunomide		2.0	1	347	47.14	8.4
Cladribine		2.0	1	347	47.14	8.4
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		8.0	2	358	66.11	48.8
Natalizumab		7.0	2	358	70.27	45.3
Daclizumab		1.0	N.M.	358	36.96	3.4
Corticosteroids		32.0	8	7	13.85	0.6
Methylprednisolone		25.0	6	5	17.60	0.6
Other corticosteroids		7.0	2	14	0.34	N.M.
Oral immunomodulators		11.0	3	347	47.81	47.0
FTY-720		7.0	2	347	48.20	30.2
BG-12		2.0	1	347	47.14	8.4
Laquinimod		2.0	1	347	47.14	8.4

(continued)

Table B-8 (cont.)

Assumptions Behind the 2020 Relapsing-Remitting Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/Year	Price/ Day ($)	Sales ($MM)
Japan	4					
Recombinant interferons		73.0	3	329	34.40	34.4
IFN-β-1b		36.0	1	329	31.47	15.5
IFN-β-1a (Avonex)		37.0	2	329	37.25	18.9
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		2.0	N.M.	358	1.17	N.M.
Mitoxantrone		1.0	N.M.	358	2.05	N.M.
Cyclophosphamide		1.0	N.M.	358	0.28	N.M.
Methotrexate		—	—	—	—	—
Oral immunosuppressants		1.0	N.M.	292	2.23	N.M.
Azathioprine		1.0	N.M.	292	2.23	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		8.0	N.M.	358	65.27	7.8
Natalizumab		8.0	N.M.	358	65.27	7.8
Daclizumab		—	—	—	—	—
Corticosteroids		51.0	2	7	15.46	0.2
Methylprednisolone		38.0	2	5	20.75	0.2
Other corticosteroids		13.0	1	14	—	—
Oral immunomodulators		1.0	N.M.	347	62.43	0.9
FTY-720		1.0	N.M.	347	62.43	0.9
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-9

Assumptions Behind the 2005 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
United States	50					
Recombinant interferons		82.0	41	329	36.31	489.1
IFN-β-1b		44.0	22	329	34.51	249.5
IFN-β-1a (Avonex)		31.0	16	329	36.90	187.9
IFN-β-1a (Rebif)		7.0	4	329	45.00	51.8
Altered peptide ligands		7.0	4	329	37.71	43.4
Glatiramer acetate		7.0	4	329	37.71	43.4
MBP-8298		—	—	—	—	—
Chemotherapeutics		15.5	8	351	7.29	20.2
Mitoxantrone		8.0	4	358	13.52	19.3
Cyclophosphamide		6.0	3	358	0.74	0.8
Methotrexate		1.5	1	292	0.24	0.1
Oral immunosuppressants		4.0	2	283	6.58	3.5
Azathioprine		3.0	2	292	2.30	1.0
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		1.0	1	256	19.40	2.5
Monoclonal antibodies		0.1	N.M.	358	56.75	1.0
Natalizumab		0.1	N.M.	358	56.75	1.0
Daclizumab		—	—	—	—	—
Corticosteroids		36.0	18	7	6.94	0.6
Methylprednisolone		28.0	14	5	8.89	0.6
Other corticosteroids		8.0	4	14	0.10	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
8G-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
France	5					
Recombinant interferons		55.0	3	329	37.63	37.1
IFN-β-1b		35.0	2	329	37.47	23.5
IFN-β-1a (Avonex)		9.0	N.M.	329	37.55	6.1
IFN-β-1a (Rebif)		11.0	1	329	38.22	7.5
Altered peptide ligands		2.0	N.M.	329	35.96	1.3
Glatiramer acetate		2.0	N.M.	329	35.96	1.3
MBP-8298		—	—	—	—	—
Chemotherapeutics		29.5	2	342	2.35	1.4
Mitoxantrone		17.0	1	358	3.86	1.3
Cyclophosphamide		5.5	N.M.	358	0.56	0.1
Methotrexate		7.0	N.M.	292	0.10	N.M.

(continued)

Table B-9 (cont.)

Assumptions Behind the 2005 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		14.0	1	266	9.48	1.9
Azathioprine		4.0	N.M.	292	1.09	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		10.0	1	256	12.84	1.8
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		30.0	2	6	20.26	0.2
Methylprednisolone		25.0	1	5	24.20	0.2
Other corticosteroids		5.0	N.M.	14	0.54	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Germany	9					
Recombinant interferons		43.0	4	329	45.91	55.5
IFN-β-1b		24.0	2	329	43.40	29.3
IFN-β-1a (Avonex)		9.0	1	329	43.27	10.9
IFN-β-1a (Rebif)		10.0	1	329	54.32	15.3
Altered peptide ligands		5.0	N.M.	329	40.82	5.7
Glatiramer acetate		5.0	N.M.	329	40.82	5.7
MBP-8298		—	—	—	—	—
Chemotherapeutics		37.0	3	349	2.62	3.0
Mitoxantrone		26.0	2	358	3.60	2.9
Cyclophosphamide		6.0	1	358	0.45	0.1
Methotrexate		5.0	N.M.	292	0.16	N.M.
Oral immunosuppressants		6.0	1	292	2.20	0.3
Azathioprine		6.0	1	292	2.20	0.3
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		42.0	4	6	24.14	0.4
Methylprednisolone		37.0	3	5	27.35	0.4
Other corticosteroids		5.0	N.M.	14	0.36	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-9 (cont.)

Assumptions Behind the 2005 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Italy	4					
Recombinant interferons		39.0	1	329	35.46	17.0
IFN-β-1b		33.0	1	329	34.38	13.9
IFN-β-1a (Avonex)		2.0	N.M.	329	33.98	0.8
IFN-β-1a (Rebif)		4.0	N.M.	329	45.07	2.2
Altered peptide ligands		3.0	N.M.	329	31.12	1.1
Glatiramer acetate		3.0	N.M.	329	31.12	1.1
MBP-8298		—	—	—	—	—
Chemotherapeutics		31.0	1	332	0.84	0.3
Mitoxantrone		12.0	N.M.	358	1.98	0.3
Cyclophosphamide		7.0	N.M.	358	0.23	N.M.
Methotrexate		12.0	N.M.	292	0.06	N.M.
Oral immunosuppressants		4.0	N.M.	292	0.89	N.M.
Azathioprine		4.0	N.M.	292	0.89	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		42.0	2	6	13.49	0.1
Methylprednisolone		36.0	1	5	15.65	0.1
Other corticosteroids		6.0	N.M.	14	0.52	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Spain	3					
Recombinant interferons		73.0	2	329	41.49	29.4
IFN-β-1b		48.0	1	329	38.58	18.0
IFN-β-1a (Avonex)		9.0	N.M.	329	37.88	3.3
IFN-β-1a (Rebif)		16.0	N.M.	329	52.23	8.1
Altered peptide ligands		2.0	N.M.	329	35.30	0.7
Glatiramer acetate		2.0	N.M.	329	35.30	0.7
MBP-8298		—	—	—	—	—
Chemotherapeutics		10.0	N.M.	331	3.49	0.4
Mitoxantrone		5.0	N.M.	358	6.93	0.4
Cyclophosphamide		1.0	N.M.	358	0.19	N.M.
Methotrexate		4.0	N.M.	292	0.02	N.M.

(continued)

Table B-9 (cont.)

Assumptions Behind the 2005 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		6.0	N.M.	292	0.57	N.M.
Azathioprine		6.0	N.M.	292	0.57	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		30.0	1	6	9.50	N.M.
Methylprednisolone		25.0	1	5	11.33	N.M.
Other corticosteroids		5.0	N.M.	14	0.35	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
United Kingdom	**2**					
Recombinant interferons		21.0	N.M.	329	38.00	4.1
IFN-β-1b		10.0	N.M.	329	31.69	1.6
IFN-β-1a (Avonex)		5.0	N.M.	329	37.95	1.0
IFN-β-1a (Rebif)		6.0	N.M.	329	48.56	1.5
Altered peptide ligands		2.0	N.M.	329	30.99	0.3
Glatiramer acetate		2.0	N.M.	329	30.99	0.3
MBP-8298		—	—	—	—	—
Chemotherapeutics		7.0	N.M.	339	1.34	0.1
Mitoxantrone		4.0	N.M.	358	2.22	N.M.
Cyclophosphamide		1.0	N.M.	358	0.37	N.M.
Methotrexate		2.0	N.M.	292	0.08	N.M.
Oral immunosuppressants		2.0	N.M.	292	1.35	N.M.
Azathioprine		2.0	N.M.	292	1.35	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		60.0	1	6	17.75	0.1
Methylprednisolone		55.0	1	5	19.34	0.1
Other corticosteroids		5.0	N.M.	14	0.30	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-9 (cont.)

Assumptions Behind the 2005 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Japan	0					
Recombinant interferons		60.0	N.M.	329	42.75	3.4
IFN-β-1b		60.0	N.M.	329	42.75	3.4
IFN-β-1a (Avonex)		—	—	—	—	—
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		10.0	N.M.	351	2.21	N.M.
Mitoxantrone		5.0	N.M.	358	3.95	N.M.
Cyclophosphamide		4.0	N.M.	358	0.54	N.M.
Methotrexate		1.0	N.M.	292	0.23	N.M.
Oral immunosuppressants		4.0	N.M.	292	4.21	N.M.
Azathioprine		4.0	N.M.	292	4.21	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		68.0	N.M.	7	32.64	N.M.
Methylprednisolone		50.0	N.M.	5	44.39	N.M.
Other corticosteroids		18.0	N.M.	14	—	—
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-10

Assumptions Behind the 2010 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
United States	55					
Recombinant interferons		80.0	44	329	37.99	550.1
IFN-β-1b		40.0	22	329	35.03	253.6
IFN-β-1a (Avonex)		25.0	14	329	36.90	167.0
IFN-β-1a (Rebif)		15.0	8	329	47.71	129.5
Altered peptide ligands		6.0	3	329	38.28	41.6
Glatiramer acetate		6.0	3	329	38.28	41.6
MBP-8298		—	—	—	—	—
Chemotherapeutics		12.0	7	352	5.94	14.0
Mitoxantrone		7.0	4	358	9.73	13.4
Cyclophosphamide		4.0	2	358	0.73	0.6
Methotrexate		1.0	1	292	0.24	N.M.
Oral immunosuppressants		3.0	2	280	7.52	3.3
Azathioprine		2.0	1	292	2.30	0.7
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		1.0	1	256	17.95	2.5
Monoclonal antibodies		2.0	1	358	42.91	16.9
Natalizumab		1.0	1	358	56.75	11.2
Daclizumab		1.0	1	358	29.06	5.7
Corticosteroids		35.0	19	7	6.88	0.7
Methylprednisolone		27.0	15	5	8.89	0.6
Other corticosteroids		8.0	4	14	0.10	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
France	6					
Recombinant interferons		55.0	3	329	37.05	39.0
IFN-β-1b		31.0	2	329	36.24	21.5
IFN-β-1a (Avonex)		9.0	1	329	36.05	6.2
IFN-β-1a (Rebif)		15.0	1	329	39.33	11.3
Altered peptide ligands		1.0	N.M.	329	36.14	0.7
Glatiramer acetate		1.0	N.M.	329	36.14	0.7
MBP-8298		—	—	—	—	—
Chemotherapeutics		24.0	1	344	2.32	1.2
Mitoxantrone		14.0	1	358	3.75	1.1
Cyclophosphamide		5.0	N.M.	358	0.54	0.1
Methotrexate		5.0	N.M.	292	0.09	N.M.

(continued)

Table B-10 (cont.)

Assumptions Behind the 2010 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		13.0	1	264	10.12	2.0
Azathioprine		3.0	N.M.	292	1.05	0.1
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		10.0	1	256	12.84	1.9
Monoclonal antibodies		1.0	N.M.	358	48.45	1.0
Natalizumab		1.0	N.M.	358	48.45	1.0
Daclizumab		—	—	—	—	—
Corticosteroids		30.0	2	6	18.74	0.2
Methylprednisolone		25.0	1	5	22.39	0.2
Other corticosteroids		5.0	N.M.	14	0.51	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Germany	11					
Recombinant interferons		47.0	5	329	45.68	75.2
IFN-β-1b		22.0	2	329	41.55	32.0
IFN-β-1a (Avonex)		11.0	1	329	41.11	15.8
IFN-β-1a (Rebif)		14.0	1	329	55.77	27.4
Altered peptide ligands		3.0	N.M.	329	41.02	4.3
Glatiramer acetate		3.0	N.M.	329	41.02	4.3
MBP-8298		—	—	—	—	—
Chemotherapeutics		29.0	3	351	2.52	2.8
Mitoxantrone		22.0	2	358	3.23	2.7
Cyclophosphamide		4.0	N.M.	358	0.36	0.1
Methotrexate		3.0	N.M.	292	0.16	N.M.
Oral immunosuppressants		4.0	N.M.	292	2.19	0.3
Azathioprine		4.0	N.M.	292	2.19	0.3
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		1.0	N.M.	358	53.28	2.0
Natalizumab		1.0	N.M.	358	53.28	2.0
Daclizumab		—	—	—	—	—
Corticosteroids		42.0	4	6	16.91	0.4
Methylprednisolone		37.0	4	5	19.15	0.4
Other corticosteroids		5.0	1	14	0.34	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
8G-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-10 (cont.)

Assumptions Behind the 2010 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Italy	5					
Recombinant interferons		42.0	2	329	35.63	23.2
IFN-β-1b		30.0	1	329	33.25	15.5
IFN-β-1a (Avonex)		4.0	N.M.	329	32.62	2.0
IFN-β-1a (Rebif)		8.0	N.M.	329	46.05	5.7
Altered peptide ligands		2.0	N.M.	329	31.27	1.0
Glatiramer acetate		2.0	N.M.	329	31.27	1.0
MBP-8298		—	—	—	—	—
Chemotherapeutics		22.0	1	337	0.95	0.4
Mitoxantrone		10.0	N.M.	358	1.94	0.3
Cyclophosphamide		5.0	N.M.	358	0.22	N.M.
Methotrexate		7.0	N.M.	292	0.06	N.M.
Oral immunosuppressants		2.0	N.M.	292	0.87	N.M.
Azathioprine		2.0	N.M.	292	0.87	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		1.0	N.M.	358	54.19	0.9
Natalizumab		1.0	N.M.	358	54.19	0.9
Daclizumab		—	—	—	—	—
Corticosteroids		42.0	2	6	13.28	0.1
Methylprednisolone		36.0	2	5	15.44	0.1
Other corticosteroids		6.0	N.M.	14	0.29	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Spain	3					
Recombinant interferons		73.0	2	329	41.13	31.8
IFN-β-1b		45.0	1	329	37.31	17.8
IFN-β-1a (Avonex)		10.0	N.M.	329	36.37	3.9
IFN-β-1a (Rebif)		18.0	1	329	53.32	10.2
Altered peptide ligands		2.0	N.M.	329	35.48	0.8
Glatiramer acetate		2.0	N.M.	329	35.48	0.8
MBP-8298		—	—	—	—	—
Chemotherapeutics		7.0	N.M.	339	3.68	0.3
Mitoxantrone		4.0	N.M.	358	6.38	0.3
Cyclophosphamide		1.0	N.M.	358	0.17	N.M.
Methotrexate		2.0	N.M.	292	0.02	N.M.

(continued)

Table B-10 (cont.)

Assumptions Behind the 2010 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		4.0	N.M.	292	0.54	N.M.
Azathioprine		4.0	N.M.	292	0.54	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		1.0	N.M.	358	48.45	0.6
Natalizumab		1.0	N.M.	358	48.45	0.6
Daclizumab		—	—	—	—	—
Corticosteroids		30.0	1	6	9.20	N.M.
Methylprednisolone		25.0	1	5	10.97	N.M.
Other corticosteroids		5.0	N.M.	14	0.33	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
United Kingdom	4					
Recombinant interferons		24.0	1	329	36.97	11.9
IFN-β-1b		9.0	N.M.	329	29.44	3.5
IFN-β-1a (Avonex)		7.0	N.M.	329	34.91	3.3
IFN-β-1a (Rebif)		8.0	N.M.	329	47.24	5.1
Altered peptide ligands		2.0	N.M.	329	29.97	0.8
Glatiramer acetate		2.0	N.M.	329	29.97	0.8
MBP-8298		—	—	—	—	—
Chemotherapeutics		5.0	N.M.	345	1.34	0.1
Mitoxantrone		3.0	N.M.	358	2.12	0.1
Cyclophosphamide		1.0	N.M.	358	0.26	N.M.
Methotrexate		1.0	N.M.	292	0.08	N.M.
Oral immunosuppressants		1.0	N.M.	292	1.13	N.M.
Azathioprine		1.0	N.M.	292	1.13	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		1.0	N.M.	358	48.13	0.7
Natalizumab		1.0	N.M.	358	48.13	0.7
Daclizumab		—	—	—	—	—
Corticosteroids		60.0	2	6	16.69	0.2
Methylprednisolone		55.0	2	5	18.18	0.2
Other corticosteroids		5.0	N.M.	14	0.32	N.M.
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-10 (cont.)

Assumptions Behind the 2010 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Japan	0					
Recombinant interferons		60.0	N.M.	329	43.02	4.2
IFN-β-1b		55.0	N.M.	329	42.75	3.8
IFN-β-1a (Avonex)		5.0	N.M.	329	46.01	0.4
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		8.0	N.M.	349	1.81	N.M.
Mitoxantrone		4.0	N.M.	358	3.23	N.M.
Cyclophosphamide		3.0	N.M.	358	0.44	N.M.
Methotrexate		1.0	N.M.	292	0.22	N.M.
Oral immunosuppressants		3.0	N.M.	292	3.43	N.M.
Azathioprine		3.0	N.M.	292	3.43	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		—	—	—	—	—
Natalizumab		—	—	—	—	—
Daclizumab		—	—	—	—	—
Corticosteroids		56.0	N.M.	7	25.02	N.M.
Methylprednisolone		40.0	N.M.	5	35.03	N.M.
Other corticosteroids		16.0	N.M.	14	—	—
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-11

Assumptions Behind the 2015 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
United States	60					
Recombinant interferons		73.0	44	329	39.23	565.0
IFN-β-1b		35.0	21	329	36.61	252.8
IFN-β-1a (Avonex)		17.0	10	329	34.13	114.5
IFN-β-1a (Rebif)		21.0	13	329	47.71	197.7
Altered peptide ligands		9.0	5	354	44.42	85.2
Glatiramer acetate		1.0	1	329	39.80	7.9
MBP-8298		8.0	5	358	45.00	77.3
Chemotherapeutics		9.0	5	350	3.58	6.9
Mitoxantrone		5.0	3	358	5.95	6.4
Cyclophosphamide		3.0	2	358	0.73	0.5
Methotrexate		1.0	1	292	0.24	N.M.
Oral immunosuppressants		8.0	5	310	27.63	44.9
Azathioprine		2.0	1	292	2.30	0.8
Teriflunomide		1.0	1	347	49.50	10.3
Cladribine		3.0	2	347	49.50	30.9
Mycophenolate mofetil		2.0	1	256	9.22	2.8
Monoclonal antibodies		5.0	3	358	34.60	37.2
Natalizumab		1.0	1	358	56.75	12.2
Daclizumab		4.0	2	358	29.06	25.0
Corticosteroids		33.0	20	7	6.76	0.7
Methylprednisolone		25.0	15	5	8.89	0.7
Other corticosteroids		8.0	5	14	0.10	N.M.
Oral immunomodulators		3.0	2	347	55.00	34.4
FTY-720		3.0	2	347	55.00	34.4
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
France	6					
Recombinant interferons		55.0	3	329	37.05	40.8
IFN-β-1b		27.0	2	329	36.61	19.8
IFN-β-1a (Avonex)		9.0	1	329	33.61	6.0
IFN-β-1a (Rebif)		19.0	1	329	39.31	14.9
Altered peptide ligands		7.0	N.M.	354	36.09	5.4
Glatiramer acetate		1.0	N.M.	329	36.64	0.7
MBP-8298		6.0	N.M.	358	36.00	4.7
Chemotherapeutics		18.0	1	347	2.35	0.9
Mitoxantrone		11.0	1	358	3.63	0.9
Cyclophosphamide		4.0	N.M.	358	0.52	N.M.
Methotrexate		3.0	N.M.	292	0.09	N.M.

(continued)

Table B-11 (cont.)

Assumptions Behind the 2015 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		16.0	1	283	18.01	5.5
Azathioprine		2.0	N.M.	292	1.00	N.M.
Teriflunomide		1.0	N.M.	347	47.47	1.0
Cladribine		3.0	N.M.	347	47.47	3.0
Mycophenolate mofetil		10.0	1	256	9.63	1.5
Monoclonal antibodies		3.0	N.M.	358	45.50	3.0
Natalizumab		1.0	N.M.	358	48.45	1.1
Daclizumab		2.0	N.M.	358	44.03	1.9
Corticosteroids		30.0	2	6	18.48	0.2
Methylprednisolone		25.0	2	5	22.08	0.2
Other corticosteroids		5.0	N.M.	14	0.48	N.M.
Oral immunomodulators		2.0	N.M.	347	48.50	2.0
FTY-720		2.0	N.M.	347	48.50	2.0
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Germany	**12**					
Recombinant interferons		50.0	6	329	44.49	91.0
IFN-β-1b		20.0	2	329	41.77	34.2
IFN-β-1a (Avonex)		14.0	2	329	36.78	21.1
IFN-β-1a (Rebif)		16.0	2	329	54.64	35.8
Altered peptide ligands		9.0	1	348	38.67	15.1
Glatiramer acetate		3.0	N.M.	329	40.64	5.0
MBP-8298		6.0	1	358	37.69	10.1
Chemotherapeutics		20.0	2	354	2.57	2.3
Mitoxantrone		17.0	2	358	2.98	2.3
Cyclophosphamide		2.0	N.M.	358	0.32	N.M.
Methotrexate		1.0	N.M.	292	0.16	N.M.
Oral immunosuppressants		6.0	1	329	35.29	9.1
Azathioprine		2.0	N.M.	292	2.19	0.2
Teriflunomide		1.0	N.M.	347	51.84	2.2
Cladribine		3.0	N.M.	347	51.84	6.7
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		3.0	N.M.	358	43.46	5.8
Natalizumab		1.0	N.M.	358	53.28	2.4
Daclizumab		2.0	N.M.	358	38.55	3.4
Corticosteroids		42.0	5	6	15.70	0.4
Methylprednisolone		37.0	5	5	17.78	0.4
Other corticosteroids		5.0	1	14	0.31	N.M.
Oral immunomodulators		2.0	N.M.	347	53.28	4.6
FTY-720		2.0	N.M.	347	53.28	4.6
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-11 (cont.)

Assumptions Behind the 2015 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Italy	5					
Recombinant interferons		46.0	3	329	36.46	30.1
IFN-β-1b		27.0	1	329	33.28	16.2
IFN-β-1a (Avonex)		6.0	N.M.	329	30.41	3.3
IFN-β-1a (Rebif)		13.0	1	329	45.85	10.7
Altered peptide ligands		6.0	N.M.	353	38.68	4.5
Glatiramer acetate		1.0	N.M.	329	30.69	0.6
MBP-8298		5.0	N.M.	358	40.28	3.9
Chemotherapeutics		17.0	1	338	0.98	0.3
Mitoxantrone		8.0	N.M.	358	1.93	0.3
Cyclophosphamide		4.0	N.M.	358	0.21	N.M.
Methotrexate		5.0	N.M.	292	0.06	N.M.
Oral immunosuppressants		4.0	N.M.	333	39.48	3.0
Azathioprine		1.0	N.M.	292	0.85	N.M.
Teriflunomide		1.0	N.M.	347	52.36	1.0
Cladribine		2.0	N.M.	347	52.36	2.0
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		2.0	N.M.	358	48.02	1.9
Natalizumab		1.0	N.M.	358	54.19	1.1
Daclizumab		1.0	N.M.	358	41.84	0.8
Corticosteroids		42.0	2	6	12.82	0.1
Methylprednisolone		36.0	2	5	14.91	0.1
Other corticosteroids		6.0	N.M.	14	0.29	N.M.
Oral immunomodulators		2.0	N.M.	347	54.20	2.1
FTY-720		2.0	N.M.	347	54.20	2.1
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Spain	3					
Recombinant interferons		73.0	3	329	41.50	34.3
IFN-β-1b		41.0	1	329	38.09	17.7
IFN-β-1a (Avonex)		12.0	N.M.	329	33.91	4.6
IFN-β-1a (Rebif)		20.0	1	329	53.05	12.0
Altered peptide ligands		7.0	N.M.	349	35.74	3.0
Glatiramer acetate		2.0	N.M.	329	34.82	0.8
MBP-8298		5.0	N.M.	358	36.11	2.2
Chemotherapeutics		5.0	N.M.	345	3.62	0.2
Mitoxantrone		3.0	N.M.	358	5.97	0.2
Cyclophosphamide		1.0	N.M.	358	0.17	N.M.
Methotrexate		1.0	N.M.	292	0.02	N.M.

(continued)

Table B-11 (cont.)

Assumptions Behind the 2015 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		5.0	N.M.	325	28.49	1.7
Azathioprine		2.0	N.M.	292	0.52	N.M.
Teriflunomide		1.0	N.M.	347	47.14	0.6
Cladribine		2.0	N.M.	347	47.14	1.1
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		2.0	N.M.	358	41.26	1.0
Natalizumab		1.0	N.M.	358	48.45	0.6
Daclizumab		1.0	N.M.	358	34.07	0.4
Corticosteroids		30.0	1	6	8.95	N.M.
Methylprednisolone		25.0	1	5	10.68	N.M.
Other corticosteroids		5.0	N.M.	14	0.32	N.M.
Oral immunomodulators		2.0	N.M.	347	48.45	1.2
FTY-720		2.0	N.M.	347	48.45	1.2
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
United Kingdom	6					
Recombinant interferons		29.0	2	329	36.17	19.2
IFN-β-1b		8.0	N.M.	329	28.56	4.2
IFN-β-1a (Avonex)		10.0	1	329	30.96	5.7
IFN-β-1a (Rebif)		11.0	1	329	46.43	9.3
Altered peptide ligands		5.0	N.M.	352	38.28	3.8
Glatiramer acetate		1.0	N.M.	329	29.39	0.5
MBP-8298		4.0	N.M.	358	40.50	3.2
Chemotherapeutics		4.0	N.M.	341	1.13	0.1
Mitoxantrone		2.0	N.M.	358	2.09	0.1
Cyclophosphamide		1.0	N.M.	358	0.25	N.M.
Methotrexate		1.0	N.M.	292	0.08	N.M.
Oral immunosuppressants		3.0	N.M.	329	31.80	1.8
Azathioprine		1.0	N.M.	292	1.13	N.M.
Teriflunomide		1.0	N.M.	347	47.14	0.9
Cladribine		1.0	N.M.	347	47.14	0.9
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		2.0	N.M.	358	42.55	1.7
Natalizumab		1.0	N.M.	358	48.13	1.0
Daclizumab		1.0	N.M.	358	36.96	0.7
Corticosteroids		60.0	3	6	16.43	0.3
Methylprednisolone		55.0	3	5	17.89	0.3
Other corticosteroids		5.0	N.M.	14	0.34	N.M.
Oral immunomodulators		2.0	N.M.	347	48.20	1.9
FTY-720		2.0	N.M.	347	48.20	1.9
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-11 (cont.)

Assumptions Behind the 2015 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Japan	1					
Recombinant interferons		60.0	N.M.	329	39.83	4.9
IFN-β-1b		50.0	N.M.	329	39.33	4.0
IFN-β-1a (Avonex)		10.0	N.M.	329	42.33	0.9
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-8298		—	—	—	—	—
Chemotherapeutics		6.0	N.M.	347	1.57	N.M.
Mitoxantrone		3.0	N.M.	358	2.81	N.M.
Cyclophosphamide		2.0	N.M.	358	0.38	N.M.
Methotrexate		1.0	N.M.	292	0.22	N.M.
Oral immunosuppressants		2.0	N.M.	292	2.95	N.M.
Azathioprine		2.0	N.M.	292	2.95	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		1.0	N.M.	358	65.27	0.1
Natalizumab		1.0	N.M.	358	65.27	0.1
Daclizumab		—	—	—	—	—
Corticosteroids		45.0	N.M.	8	19.81	N.M.
Methylprednisolone		30.0	N.M.	5	29.71	N.M.
Other corticosteroids		15.0	N.M.	14	—	—
Oral immunomodulators		—	—	—	—	—
FTY-720		—	—	—	—	—
8G-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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Source: Decision Resources, Inc.

Table B-12

Assumptions Behind the 2020 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
United States	64					
Recombinant interferons		68.0	43	329	39.50	562.4
IFN-β-1b		30.0	19	329	36.93	232.0
IFN-β-1a (Avonex)		14.0	9	329	29.43	86.3
IFN-β-1a (Rebif)		24.0	15	329	48.60	244.2
Altered peptide ligands		13.0	8	354	44.42	131.0
Glatiramer acetate		1.0	1	329	37.48	7.8
MBP-8298		12.0	8	358	45.00	123.1
Chemotherapeutics		7.0	4	350	2.39	3.8
Mitoxantrone		4.0	3	358	3.75	3.4
Cyclophosphamide		2.0	1	358	0.73	0.3
Methotrexate		1.0	1	292	0.24	N.M.
Oral immunosuppressants		10.0	6	310	31.24	68.3
Azathioprine		2.0	1	292	2.30	0.9
Teriflunomide		2.0	1	347	49.50	21.9
Cladribine		4.0	3	347	49.50	43.8
Mycophenolate mofetil		2.0	1	256	5.38	1.8
Monoclonal antibodies		6.0	4	358	33.67	46.1
Natalizumab		1.0	1	358	56.75	12.9
Daclizumab		5.0	3	358	29.06	33.1
Corticosteroids		32.0	20	7	6.70	0.7
Methylprednisolone		24.0	15	5	8.89	0.7
Other corticosteroids		8.0	5	14	0.10	N.M.
Oral immunomodulators		5.0	3	347	55.00	51.7
FTY-720		5.0	3	347	55.00	51.7
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
France	6					
Recombinant interferons		53.0	3	329	36.67	40.3
IFN-β-1b		23.0	1	329	36.16	17.3
IFN-β-1a (Avonex)		8.0	1	329	30.04	5.0
IFN-β-1a (Rebif)		22.0	1	329	39.61	18.1
Altered peptide ligands		10.0	1	354	35.71	8.0
Glatiramer acetate		1.0	N.M.	329	33.08	0.7
MBP-8298		9.0	1	358	36.00	7.3
Chemotherapeutics		12.0	1	347	2.32	0.6
Mitoxantrone		8.0	1	358	3.28	0.6
Cyclophosphamide		3.0	N.M.	358	0.51	N.M.
Methotrexate		1.0	N.M.	292	0.09	N.M.

(continued)

Table B-12 (cont.)

Assumptions Behind the 2020 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		17.0	1	283	20.66	7.3
Azathioprine		1.0	N.M.	292	0.96	N.M.
Teriflunomide		2.0	N.M.	347	47.47	2.1
Cladribine		4.0	N.M.	347	47.47	4.2
Mycophenolate mofetil		10.0	1	256	6.55	1.1
Monoclonal antibodies		4.0	N.M.	358	45.13	4.1
Natalizumab		1.0	N.M.	358	48.45	1.1
Daclizumab		3.0	N.M.	358	44.03	3.0
Corticosteroids		30.0	2	6	17.99	0.2
Methylprednisolone		25.0	2	5	21.48	0.2
Other corticosteroids		5.0	N.M.	14	0.47	N.M.
Oral immunomodulators		3.0	N.M.	347	48.50	3.2
FTY-720		3.0	N.M.	347	48.50	3.2
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Germany	14					
Recombinant interferons		51.0	7	329	44.26	100.2
IFN-β-1b		18.0	2	329	43.18	34.5
IFN-β-1a (Avonex)		15.0	2	329	34.62	23.1
IFN-β-1a (Rebif)		18.0	2	329	53.36	42.7
Altered peptide ligands		12.0	2	348	37.13	21.2
Glatiramer acetate		3.0	N.M.	329	35.47	4.7
MBP-8298		9.0	1	358	37.69	16.4
Chemotherapeutics		15.0	2	354	2.39	1.7
Mitoxantrone		13.0	2	358	2.73	1.7
Cyclophosphamide		1.0	N.M.	358	0.28	N.M.
Methotrexate		1.0	N.M.	292	0.15	N.M.
Oraf immunosuppressants		7.0	1	329	44.75	14.7
Azathioprine		1.0	N.M.	292	2.19	N.M.
Teriflunomide		2.0	N.M.	347	51.84	4.9
Cladribine		4.0	1	347	51.84	9.7
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		4.0	1	358	42.23	8.2
Natalizumab		1.0	N.M.	358	53.28	2.6
Daclizumab		3.0	N.M.	358	38.55	5.6
Corticosteroids		42.0	6	6	14.49	0.4
Methylprednisolone		37.0	5	5	16.41	0.4
Other corticosteroids		5.0	1	14	0.28	N.M.
Oral immunomodulators		3.0	N.M.	347	53.28	7.5
FTY-720		3.0	N.M.	347	53.28	7.5
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-12 (cont.)

Assumptions Behind the 2020 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Italy	6					
Recombinant interferons		50.0	3	329	36.87	36.2
IFN-β-1b		24.0	1	329	33.24	15.7
IFN-β-1a (Avonex)		8.0	N.M.	329	27.18	4.3
IFN-β-1a (Rebif)		18.0	1	329	46.01	16.3
Altered peptide ligands		9.0	1	353	38.94	7.5
Glatiramer acetate		1.0	N.M.	329	28.21	0.6
MBP-8298		8.0	N.M.	358	40.28	6.9
Chemotherapeutics		12.0	1	338	1.02	0.3
Mitoxantrone		6.0	N.M.	358	1.91	0.2
Cyclophosphamide		3.0	N.M.	358	0.21	N.M.
Methotrexate		3.0	N.M.	292	0.06	N.M.
Oral immunosuppressants		6.0	N.M.	333	43.77	5.4
Azathioprine		1.0	N.M.	292	0.83	N.M.
Teriflunomide		2.0	N.M.	347	52.36	2.2
Cladribine		3.0	N.M.	347	52.36	3.3
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		3.0	N.M.	358	45.96	3.0
Natalizumab		1.0	N.M.	358	54.19	1.2
Daclizumab		2.0	N.M.	358	41.84	1.8
Corticosteroids		42.0	3	6	12.61	0.2
Methylprednisolone		36.0	2	5	14.65	0.2
Other corticosteroids		6.0	N.M.	14	0.29	N.M.
Oral immunomodulators		3.0	N.M.	347	54.20	3.4
FTY-720		3.0	N.M.	347	54.20	3.4
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
Spain	3					
Recombinant interferons		69.0	2	329	41.70	32.9
IFN-β-1b		35.0	1	329	38.39	15.4
IFN-β-1a (Avonex)		12.0	0	329	30.31	4.1
IFN-β-1a (Rebif)		22.0	1	329	53.19	13.4
Altered peptide ligands		9.0	0	349	35.20	3.9
Glatiramer acetate		2.0	N.M.	329	32.00	0.7
MBP-8298		7.0	N.M.	358	36.11	3.1
Chemotherapeutics		4.0	N.M.	345	2.76	0.1
Mitoxantrone		2.0	N.M.	358	5.43	0.1
Cyclophosphamide		1.0	N.M.	358	0.17	N.M.
Methotrexate		1.0	N.M.	292	0.02	N.M.

(continued)

Table B-12 (cont.)

Assumptions Behind the 2020 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Oral immunosuppressants		6.0	N.M.	325	39.37	2.8
Azathioprine		1.0	N.M.	292	0.50	N.M.
Teriflunomide		2.0	N.M.	347	47.14	1.1
Cladribine		3.0	N.M.	347	47.14	1.7
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		3.0	N.M.	358	38.86	1.4
Natalizumab		1.0	N.M.	358	48.45	0.6
Daclizumab		2.0	N.M.	358	34.07	0.8
Corticosteroids		30.0	1	6	8.74	N.M.
Methylprednisolone		25.0	1	5	10.41	N.M.
Other corticosteroids		5.0	N.M.	14	0.31	N.M.
Oral immunomodulators		3.0	N.M.	347	48.45	1.8
FTY-720		3.0	N.M.	347	48.45	1.7
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—
United Kingdom	7					
Recombinant interferons		32.0	2	329	35.69	25.0
IFN-β-1b		7.0	N.M.	329	28.40	4.3
IFN-β-1a (Avonex)		11.0	1	329	27.69	6.7
IFN-β-1a (Rebif)		14.0	1	329	45.61	14.0
Altered peptide ligands		8.0	1	352	38.48	7.3
Glatiramer acetate		1.0	N.M.	329	24.34	0.5
M8P-8298		7.0	N.M.	358	40.50	6.7
Chemotherapeutics		3.0	N.M.	341	0.79	N.M.
Mitoxantrone		1.0	N.M.	358	2.05	N.M.
Cyclophosphamide		1.0	N.M.	358	0.25	N.M.
Methotrexate		1.0	N.M.	292	0.08	N.M.
Oral immunosuppressants		5.0	N.M.	329	37.94	4.4
Azathioprine		1.0	N.M.	292	1.13	N.M.
Teriflunomide		2.0	N.M.	347	47.14	2.2
Cladribine		2.0	N.M.	347	47.14	2.2
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		3.0	N.M.	358	40.68	2.9
Natalizumab		1.0	N.M.	358	48.13	1.1
Daclizumab		2.0	N.M.	358	36.96	1.8
Corticosteroids		60.0	4	6	16.16	0.3
Methylprednisolone		55.0	4	5	17.60	0.3
Other corticosteroids		5.0	N.M.	14	0.34	N.M.
Oral immunomodulators		3.0	N.M.	347	48.20	3.3
FTY-720		3.0	N.M.	347	48.20	3.3
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

(continued)

Table B-12 (cont.)

Assumptions Behind the 2020 Chronic-Progressive Multiple Sclerosis Market

	Drug-Treated Population (000s)	% of Patients Treated	Number of Patients Treated (000s)	Compliant Days of Therapy/ Year	Price/ Day ($)	Sales ($MM)
Japan	1					
Recombinant interferons		60.0	N.M.	329	32.91	4.5
IFN-β-1b		45.0	N.M.	329	31.47	3.2
IFN-β-1a (Avonex)		15.0	N.M.	329	37.25	1.3
IFN-β-1a (Rebif)		—	—	—	—	—
Altered peptide ligands		—	—	—	—	—
Glatiramer acetate		—	—	—	—	—
MBP-829B		—	—	—	—	—
Chemotherapeutics		4.0	N.M.	347	1.15	N.M.
Mitoxantrone		2.0	N.M.	358	2.05	N.M.
Cyclophosphamide		1.0	N.M.	358	0.28	N.M.
Methotrexate		1.0	N.M.	292	0.22	N.M.
Oral immunosuppressants		1.0	N.M.	292	2.23	N.M.
Azathioprine		1.0	N.M.	292	2.23	N.M.
Teriflunomide		—	—	—	—	—
Cladribine		—	—	—	—	—
Mycophenolate mofetil		—	—	—	—	—
Monoclonal antibodies		1.0	N.M.	358	65.27	0.2
Natalizumab		1.0	N.M.	358	65.27	0.2
Daclizumab		—	—	—	—	—
Corticosteroids		34.0	N.M.	8	12.21	N.M.
Methylprednisolone		20.0	N.M.	5	20.75	N.M.
Other corticosteroids		14.0	N.M.	14	—	—
Oral immunomodulators		1.0	N.M.	347	62.43	0.1
FTY-720		1.0	N.M.	347	62.43	0.1
BG-12		—	—	—	—	—
Laquinimod		—	—	—	—	—

N.M. = Not meaningful.
Note: Numbers reflect rounding.

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MULTIPLE SCLEROSIS 2005-2020

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Appendix C

Experts Interviewed

For questions regarding the report content and analysis, contact:

Analyst: Bethany A. Kiernan, Ph.D.
Tel +1.781.296.2631 ♦ E-mail bkiernan@dresources.com

Epidemiologist: Jessica Goetz Welch, M.P.H.
Tel +1.781.296.2617 ♦ E-mail jwelch@dresources.com

For questions regarding consulting, contact: Jim McDermott Tel +1.781.296.2522 ♦ E-mail jmcdermott@dresources.com

For questions regarding sales, service, and technical support, contact:

United States
Tel +1.781.296.2537 ♦ Fax +1.781.296.2550

Europe
Tel +32.2.357.06.16 ♦ Fax +32.2.351.2347

Japan
Tel +81.3.5401.2615 ♦ Fax +81.3.5401.2617

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Appendix C. Experts Interviewed—Multiple Sclerosis

Our primary research is an ongoing process. The insights we gain into the opinions and practices of leading physicians and researchers in this area derive from at least 100 interviews conducted in each therapeutic area each year. Additionally, our analysts confer with thought leaders at conferences and industry events. Further, we conduct online surveys to gain information from primary care physicians/ general practitioners and managed care representatives. Thus, our primary research relies on input from hundreds of physicians and researchers; the names listed here are of those we interviewed in depth during the most recent study period focusing on this indication.

Esteban Albea-Ristol, M.D.
Especialista en Neurología
Servicio de Neurología
Universidad de Alcala de Henares
Madrid, Spain

Julián Benito-Leon, M.D.
Professor
Departamento de Neurología
Hospital General de Móstoles
Móstoles, Spain

Abhijit Chaudhuri, M.D., Ph.D., D.M., F.A.C.P., F.R.C.P.
Consultant Neurologist
Department of Neurology
Essex Centre for Neurological Sciences
Glasgow, United Kingdom

Marinella Clerico, M.D.
Direttore
Divisione di Neurologia
Ospedale S. Luigi Gonzaga
Orbassano, Italy

Graziella Filippini, M.D.
Professore
Unita' di Neuroepidemiologia
Istituto Nazionale Neurologico "C Besta"
Milan, Italy

Peter Flachenecker, M.D.
Chefarzt
Abteilung für Neurologie
Neurologisches Rehabilitationszentrum
Quellenhof
Bad Wildbad, Germany

Kazuo Fujihara, M.D.
Associate Professor
Department of Neurology
Tohoku University Graduate School of Medicine
Miyagi, Japan

Joystone Gbadamosi, M.D.
Assistenzarzt, Mitglied der Arbeitsgruppe "Multiple Sklerose—Sprechstunde"
Neurologische Klinik mit Schwerpunkt Multiple Sklerose
Universitätskrankenhaus Hamburg-Eppendorf
Hamburg, Germany

Gavin Giovannoni, Ph.D., M.B.B.C.H., F.C.C.P.
Senior Clinical Lecturer
Department of Clinical Neurology
Institute of Clinical Neurology
London, United Kingdom

Hans-Peter Hartung, M.D., Ph.D.
Vorsitzender
Abteilung für Neurologie
Heinrich-Heine-Universität
Düsseldorf, Germany

Boris Kallmann, M.D.
Funktionsoberarzt
Abteilung für Neurologie
Neurologische Universitätsklinik
Würzburg, Germany

Dawn Langdon, Ph.D., M.A.
Academic Director
Department of Psychology
Royal Holloway University of London
Surrey, United Kingdom

Pierre Louchart, M.D.
Neurologue
Service de Neurologie
Centre Hospitalier de Dunkerque
Dunkerque, France

Daniel Mikol, M.D., Ph.D.
Director
Multiple Sclerosis Clinic
University of Michigan Medical Center
Ann Arbor, Michigan

Aaron Miller, M.D.
Medical Director
Corinne Goldsmith Dickinson Center for Multiple Sclerosis
Mt. Sinai School of Medicine
New York, New York

Sachiko Miyake, M.D., Ph.D.
Section Chief
Department of Immunology
National Institute of Neuroscience, National Center of Neurology and Psychiatry
Tokyo, Japan

Pedro Jesus Modrego, M.D.
Medico Adjunto
Servicio de Neurología
Hospital Miguel Servet
Zaragoza, Spain

Thibault Moreau, M.D., Ph.D.
Neurologue Adjoint
Clinique de Neurologie
Hôpital Général de Dijon
Dijon, France

Kyoichi Nomura, M.D.
Professor
Department of Neurology
Saitama Medical Center
Saitama, Japan

Kohei Ohta, M.D.
Assistant Professor
Department of Neurology
Tokyo Women's Medical University
Tokyo, Japan

Francesco Patti, M.D.
Professore
Dipartimento di Neuroscienze
Universita' di Catania
Catania, Italy

Dieter Poehlau, M.D.
Chefarzt
Abteilung für Neurologie
Kamillus Klinik
Asbach, Germany

Peter Rieckmann, M.D.
Oberarzt
Neurochirugische Universitätsklinik
Julius-Maximilians-Universität
Würzburg, Germany

Victor M. Rivera, M.D.
Medical Director
Maxine Mesinger Multiple Sclerosis Clinic
Professor of Neurology
Department of Neurology
Baylor College of Medicine Multiple Sclerosis Center
Houston, Texas

Moses Rodriguez, M.D.
Professor of Immunology and Neurology
Division of Neuroimmunology
Department of Neurology
Mayo Clinic
Rochester, Minnesota

Marco Rovaris, M.D.
Dirigente Medico Neurologo
Dipartimento di Neurologia
Ospedale San Raffaele
Milan, Italy

Jaume Sastre-Garriga, M.D.
Director Mèdic
Unitat de Neurología
Hospitals de Dia--Fundació Esclerosi Múltiple
Barcelona, Spain

Mohammad Sharief, Ph.D., M.B., Ch.B., F.R.C.P.
Senior Lecturer and Consultant Neurologist
Department of Clinical Neurosciences
Guy's Hospital
London, United Kingdom

Stefano Sotgiu, M.D.
Ricercatore Universitario Confermato
Istituto di Clinica Neurologica
Universita' di Sassari
Sassari, Italy

Bruno Stankoff, M.D.
Praticien Attaché
Fédération de Neurologie
Hôpital Pitié Salpêtrière
Paris, France

Lawrence Steinman, M.D.
Professor of Neurological Sciences, Chair
Interdepartmental Program in Immunology
Department of Neurological Sciences
Beckman Center for Molecular Medicine
Stanford University
Stanford, California

Olaf Stuve, M.D.
Assistant Professor
Department of Neurology
University of Texas Southwestern
Dallas, Texas

Patrick Vermersch, M.D., Ph.D.
Professeur de Neurologie
Clinique de Neurologie
Hôpital Roger Salengro
Lille, France

Timothy Vollmer, M.D.
Chairman
Division of Neurology
Barrow Neurological Institute
Phoenix, Arizona

About the Authors

Bethany A. Kiernan, Ph.D., is a research analyst in the central nervous system disorders group at Decision Resources, Inc. Prior to joining the company, Dr. Kiernan was a postdoctoral associate at Tufts University School of Medicine, where she studied the development of specific neuron-muscle connections. She earned a Ph.D. in neurosciences from Case Western Reserve University, where she conducted research on the role of the nervous system in healing skin wounds. She holds a B.A. in biology from the College of the Holy Cross.

Jonathan W. Searles is a research associate in the central nervous system disorders unit of Decision Resources, Inc. Prior to joining Decision Resources, Mr. Searles received a B.A. degree, summa cum laude, from Brandeis University. While earning his bachelor of arts degree, Mr. Searles conducted research projects at the Harvard University Peabody Museum and at Brandeis.

Jessica Goetz Welch, M.P.H., is an epidemiologist at Decision Resources, Inc. Previously, she investigated quality-of-life outcomes among epileptic children in the United States and worked as a research assistant for the California Air Resources Board, where she evaluated the quality and availability of health-related datasets. She holds a B.S. in applied psychology from New York University and an M.P.H. in epidemiology from the University of Michigan's School of Public Health.

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For more information, including telephone access to analysts, please contact:

United States: *Robert Fucile*
Telephone +1.781.296.2537
Telefax +1.781.296.2550
E-mail rfucile@dresources.com

Europe: *Vera Bisegna*
Telephone +32.2.357.06.16
Telefax +32.2.351.2347
E-mail vbisegna@decisionresources.be

Japan: *Makiko Yoshimoto*
Telephone +81.3.5401.2615
Telefax +81.3.5401.2617
E-mail makiko@dresources.jp

Or visit our World Wide Web site at www.decisionresources.com.

Cognos

Principal Director
Kate W. Hohenberg, M.A.

Research Analysts
Amy Jassen, Ph.D. • Julie Kerner, Ph.D.
Bethany A. Kiernan, Ph.D. • Nitasha Manchanda, Ph.D.
Nathalie C. Taylor, Ph.D. • Andrea S. Witt, Ph.D.

Associate Analysts
Maria Marzilli • Jonathan Searles

Research Associate
Andrew N. Deslaurier, M.S.

Epidemiology
Michael McGuill, M.P.H., D.V.M., Principal Director
Marguerite Dresser, M.S., Senior Epidemiologist
Brian Dreyfus, M.P.H., Epidemiologist
Jill Dreyfus, M.P.H., Senior Epidemiologist
Claire Herman, M.P.H., Epidemiologist II
Michael Hughes, Ph.D., Epidemiologist II
Prachi Vora, M.P.H., Epidemiologist II
Jessica Goetz Welch, M.P.H., Epidemiologist I
Gladys Ting, M.S., Epidemiologist II
Catherine Vasilakis-Scaramozza, M.P.H., Epidemiologist I, Ph.D. candidate

London Office
Stuart Harper, Manager

Tokyo Office
Hiroshi Tashiro, Manager
Motoko Ushiku, M.P.H., Researcher • Michi Yamauchi, Researcher
Yoko Aso, Research Associate

Research Services
Shelley P. Maes, Manager
Shachi Shrestha, Research Coordinator, Waltham
Heather Tighe, Research Coordinator, Waltham
Marylou Bosco, Senior Research Coordinator, London
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