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Features

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In MS, a crop of orals has joined the older established therapies, yielding new options—and fierce competition. One thing they can all agree on: there's been a transformation of the treatment landscape in just the last three years. ***Noah Pines*** *reports*

Biogen CEO cautions on Tecfidera EU launch

As the number of multiple sclerosis (MS) cases rises worldwide, revolutionary advancements in treatment are paying clinical dividends to patients. With this past spring's US launch of Biogen Idec's Tecfidera (dimethyl fumarate), there are now a total of three oral agents indicated for relapsing remitting forms of a disease that affects an estimated 300,000-350,000 people in the US and about 2 million worldwide.

"Until a [few] years ago, patients had only two options: Copaxone or interferon. They are injectable, unwieldy and not particularly effective. People are very excited about the oral drugs, especially Tecfidera, which appears to be the best in terms of effectiveness, safety and convenience," says Ben Weintraub, PhD, principal of *in*Thought Research, part of Symphony Health Solutions. "It was prescribed to people just starting therapy in its second week on the market, which I have never seen in an MS drug launch before."

And, after its first six months on the market, Tecfidera has become the No.-1 oral MS treatment in terms of patients on therapy in the US, according to Richard Francis, SVP, US commercial, Biogen Idec, citing IMS data. "This is a major achievement given that we launched as the third oral in a highly competitive market," boasts Francis.

To see a chart of the Top 50 neurology products for 2012, click here

Indeed, Tecfidera's introduction heats up an oral MS market that had already included Novartis's Gilenya (fingolimod) and Sanofi/Genzyme's Aubagio (teriflunomide). Analysts attribute Tecfidera's meteoric blastoff to its safety profile. While it has not been associated with any heart attacks, Gilenya requires cardiac monitoring after the first dose; and Aubagio is associated with potential liver effects that require monitoring.

"Patients tell us their physicians said that Tecfidera is as efficacious but offers better safety compared to Gilenya, which is why it has a precipitous launch curve," notes Michael Fronstin, general manager of the health outcomes group at Kantar Health. "Further, at the recent ECTRIMS meeting in Copenhagen, they looked at data showing four years of evidence [during which] Tecfidera maintained its efficacy with no new safety issues or side effects."

Gilenya was first in the race to sell an MS capsule, launching in September 2010. “The orals are soon to account for 20% of the market, and that's a quick transformation in just three years,” observes Dagmar Rosa-Bjorkeson, who leads the MS business unit at Novartis.

It's come at a good time. The Multiple Sclerosis International Federation's Atlas of MS 2013 showed last month the number of people living with the disease rose 10% over the past five years to 2.3 million people worldwide.

More treatments are on the way, but Tecfidera, as a result of its profile, is currently poised to rule the MS market. Sales in its first quarter on the market were $192 million, about three times beyond the average Wall Street expectations. Its launch has not been without challenges. A 59-year old woman who had received Tecfidera died in July; however, an investigation by the company found it unlikely that her death was linked to the medication.

The next hurdle Tecfidera will face is EU approval, where the company is working with regulatory authorities to seek clarity on regulatory data protection (RDP) for the product. RDP prevents generic drug companies from using regulatory submissions and clinical data until expiration of the granted period of exclusivity. “While the Gilenya patent is secure for quite a while, Aubagio had some problems getting exclusivity,” says Weintraub. “Biogen Idec hasn't launched there yet, but they want to make sure they're in a secure commercial position.”

Novartis isn't taking all this lying down, countering with its trove of real-world evidence as well as its having better access. Fronstin notes that Kantar Health's own research shows Gilenya reimbursement has improved since launch, when 40% of users were having access issues. “This may be less of a problem now than it was a year ago,” he says.

While Tecfidera and its oral brethren haven't yet triggered a wholesale collapse in Copaxone, interferon and Tysabri business, they are certainly muting continued growth of the older drugs. Unlike hepatitis C, where there is an ocean of untreated patients, there are a limited number of people with MS, meaning that the orals will drain sales from the big drugs in the category. That and the availability next year of generic Copaxone and, shortly thereafter, biosimilar interferons, all will give payers more leverage to stem cost increases.

Physicians' safety expectations created by Tecfidera also are likely to reframe their receptivity to the next market entrant, Sanofi's Lemtrada (alemtuzumab), which gained EU approval in September. Although Lemtrada “appears to cure MS—you can take this drug once and in a good proportion of people, their MS does not come back,” says Weintraub—there are both safety concerns and lack of efficacy in people with severe disease. “The Catch-22 is that those who benefit most have early disease, but those are the patients in which you don't want to use a risky drug.” Lemtrada was a key asset in Sanofi's acquisition of Genzyme, and is currently under review by the FDA.

Besides Tecfidera, the other challenge that Sanofi faces is that drug launches in Europe are snail slow. Although approvals are centralized, funding decisions are not, which creates resource-intensive country-by-country value dossier presentations to increasingly scrutinizing cost-effectiveness committees. Contrast this to the US system there FDA approval is the green light to start shipping product to the pharmacy.

Other areas of neurology, especially Alzheimer's disease, have not panned out as well as MS. “This could have been a very exciting year for Alzheimer's disease, but it is not. There is no larger unmet need than Alzheimer's disease, and it is encouraging that no one is giving up,” opines Weintraub.

Last year, the two most advanced compounds in development for AD, Pfizer's bapineuzumab and Eli Lilly's solanezumab, both missed their Phase III primary endpoints (both cognitive and functional). Although bapi was shut down, Lilly continues to develop solanezumab because it demonstrated a statistically significant improvement in cognition when the data from mild patients in both Phase III trials were combined.

In a recent research note, the Bernstein senior analyst Dr. Tim Anderson commented, “This is consistent with the theory that treatments for Alzheimer's will need to be given as early in the course of disease as possible in order for them to be maximally effective.” The analyst put the overall odds of technical success for sola below 50%.

Lilly's next Phase III trial of sola, EXPEDITION III, will look only at mild AD patients and is likely to entail 18 months of dosing. And, despite Lilly's BACE inhibitor failure, Merck continues to study its BACE inhibitor in Alzheimer's disease.

CLINICAL CORNER

One of the most closely watched medical stories of 2012 was the development of medications for Alzheimer's, a disease affecting 5 million Americans and a leading cause of death in the US. Unfortunately the two drug candidates, Pfizer's bapineuzumab and Eli Lilly's solanezumab, missed their Phase III cognitive and functional primary endpoints. However, the industry is not giving up on its quest to corral and ultimately conquer this deadly and debilitating disease.

"Companies are now looking at the potential precursors of Alzheimer's, such as mild cognitive impairment (MCI) and age-associated memory impairment (AAMI) as potential avenues of therapeutic targeting," says Dr. Thomas Hochadel (pictured at left), chief operating officer and co-founder of Cognitive Research Corporation, a boutique CRO focused on neurology and psychiatry. "It has been harder to show an effect in the moderate or severe patients, so companies are looking at incipient syndromes."

Additionally, his clients are seeking to develop indications for the various behavioral symptoms of Alzheimer's disease. "They are looking at things like agitation, depression, and other behavioral disturbances within the AD patient population to see if they can effectively control some of the day-to-day symptoms."

While looking at early cognitive symptoms and chipping away at the behavioral symptoms seems to make sense, the big challenge is the regulatory hurdle. "No one has ever gotten an indication in MCI or AAMI," explains Dr. Hochadel. "The agency has offered some input, but whether you're looking at the cognitive side or the behavioral side of these disorders, it can still be hard to show an impact. You need a large patient sample to show a small change in cognition."

Cognitive Research Corp., founded by Dr. Hochadel with former Navy psychologist Gary Kay, PhD, has re-tasked a driving simulator program developed in conjunction with the University of Iowa's world-renowned National Advanced Driving Simulator to use as part of their clinical cognitive research. Their 16 "MiniSim" simulators, using exclusively licensed software from the NADS, have been used in pharmaceutical clinical trials. "Driving provides us with an exceptionally good measure of cognitive and psychomotor functioning," said Dr. Kay.

Driving impairment from medication is an underappreciated menace, Dr. Kay told MM&M in an earlier interview, noting that diphenhydramine, the active ingredient in Benadryl, can have the same effect on drivers as a .07 blood alcohol level. Kay's firm did a study of the effects of obstructive sleep apnea on driving for Provigil/Nuvigil maker Cephalon (now Teva) and found "significant improvement" in performance for sufferers using the drug or CPAP machines. They've also studied ADHD's effects on driving for Shire, looked at sleep deprivation and Alzheimer's-related agitation for other clients, even tested foods, beverages and nutriceuticals. They expect to benefit from marijuana legalization bills pending in state legislatures.

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