Second oral MS drug wins FDA nod

Biogen Idec's oral multiple sclerosis (MS) drug Tecfidera (dimethyl fumarate) represents one of the most unusual major product launches in recent years. Formerly known as BG-12, Tecfidera was approved on March 27 by the US Food and Drug Administration (FDA)—and is likely to be approved soon by the European Commission. It comes with a hefty annual price tag of $54,900 in the US and has attracted multibillion dollar revenue forecasts because of its promising phase 3 data, which suggest it offers patients an attractive combination of efficacy and safety.

Cambridge, Massachusetts–based Biogen Idec has yet to conduct head-to-head studies of Tecfidera against other drugs, but it appears to offer an intermediate level of efficacy. It is superior to the older injectables, which include three different interferon-beta1a products and Petach Tikva, Israel–based Teva's Copaxone (glatiramer acetate) (collectively referred to as the ABCR drugs; Avonex, Betaseron, Copaxone and Rebif) but less potent—though much safer—than either the $\alpha_4\beta_1$-integrin inhibitor Tysabri, the oral sphingosine-1-phosphate (S1P) receptor agonist Gilenya (fingolimod), marketed by Basel-based Novartis or aleumtuzumab (Lemtrada). Aleumtuzumab is an anti-CD52 antibody still under FDA review, after its developer, the Genzyme unit of Paris-based Sanofi, received a refusal-to-file letter last year.

Although there is some evidence that Tecfidera, a simple and tiny small molecule, may work by activating the cytoprotective nuclear factor erythroid 2–related factor 2 (Nrf2)-signaling pathway, which has anti-inflammatory and anti-oxidative effects, its precise molecular target and mechanism of action remain unclear. In that respect, it resembles the older generation of injectable drugs, including the ABCR drugs. However, its efficacy and tolerability profile sets it apart from these products.

AP Photo/Steven Senne

Biogen Idec's Tecfidera is the second MS drug available as a pill following Novartis' Gilenya.

Reports from Germany of several cases of progressive multifocal leukoencephalopathy (PML) in psoriasis patients on a related drug, Fumaderm (fumaric acid esters), are unlikely to derail adoption of Tecfidera.

The risk of PML, an often fatal demyelinating condition caused by John Cunningham (JC) virus infection in the brain, is the reason why Tysabri (natalizumab), also marketed by Biogen Idec, remains a second-line therapy in MS. The association between PML and Tecfidera is more indirect, however, and Ralf Gold, professor of neurology at the Ruhr-University, Bochum, Germany, says he does not expect problems with the drug. "The Fumaderm story will be reported in a letter to the *NEJM* [the *New England Journal of Medicine*], without any reference to BG-12," says Gold, who was senior author on a report of a pivotal trial for Tecfidera (*New Engl. J. Med.* **367**, 1098–1107, 2012). "Yet the competitors of Biogen [will] try to make this a big point—for marketing," he adds.

In two cases in which PML occurred in patients on Fumaderm monotherapy, clinicians violated treatment guidelines. "Despite low lymphocytes, with values less than 300 [cells per cubic milliliter], medication was not stopped but continued," Gold says. In another case, other risk factors were also present. A spokeswoman for Biogen Idec, of Cambridge, Massachusetts, says Tecfidera and Fumaderm are not comparable. "They are different chemical entities and used in different patient populations. There have been no cases of PML, or opportunistic infections of any kind, in Tecfidera-treated patients," she says.

Tecfidera is widely expected to become the first-line therapy of choice for new MS patients, but not necessarily for those already on other therapies. "Realistically, patients who are compliant and stable with injections will not be switched, but BG-12 offers an option for a horizontal switch in baseline therapies before escalating to fingolomid or natalizumab because it is probably superior to ABCR drugs," Gold says. It also offers a step-down option for patients on Tysabri who develop JC virus infection.

Cormac Sheridan *Dublin*

IN brief

Chronic fatigue first on FDA agenda

The US Food and Drug Administration (FDA) has chosen chronic fatigue syndrome and myalgic encephalomyelitis (CFS/ME) to be first in a series of 20 patient-focused drug development meetings funded by the Prescription Drug User Fee Act re-authorization of 2012 (PDUFA V). "This initiative in PDUFA V could lead to other longer-term efforts and collaborations that could advance drug development," says FDA spokesperson Lisa Kubaska, but "that will require further exploration with various stakeholders as we learn more about the patient perspective on specific disease areas." CFS/ME drew public attention last fall when the FDA Arthritis Advisory Committee voted 8–5 against approval for rintatolimod (Ampligen), a Toll-like receptor 3 agonist from Hemispherx Biopharma of Philadelphia. "One reason we got on the FDA radar is because there is significant unmet medical need in the CFS community," says Suzanne Vernon, scientific director of the CFS and immune deficiency advocacy group, CFIDS Association of America, in Washington, DC. "Now there's nothing in the pipeline." The FDA effort is distinct from the Patient-Centered Outcomes Research Institute (PCORI) (*Nat. Biotechnol.* **30**, 482–484, 2010). "PCORI's focus is on evaluation of therapies and services that are already available," says executive director Joe Selby, "not in research on drugs in development." As some research methods are of mutual interest, the group is having discussions with FDA on a common approach to developing patient-reported measures, he says.

Mark Ratner

IN their words

"So we are between a rock and a hard place, which is very unfortunate, because if this is an effective treatment for patients then they're obviously being denied that possibility." David Nutt, of London's Imperial College, complaining about the arcane drug laws that prevent manufacturers from testing therapeutic activities of mushrooms. Nutt believes that psilocybin is effective against depression. (*BBC,* 6 April 2013)

"There's a lot of experimental technologies out there, but if you need something that is functional, you need either Illumina or Life Tech's Ion Torrent business." Mizuho Securities analyst Peter Lawson said of Thermo Fisher's $13.6-billion purchase of Life Technologies. (*Reuters*, 15 April 2013)