

December 31, 2012

VIA HAND DELIVERY

Dockets Management Branch, HFA-305
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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Re: Citizen Petition Requesting That FDA Refrain From Approving Any New Drug for the Treatment of Multiple Sclerosis Unless and Until It Has Been Reviewed By the Appropriate Advisory Committee

Dear Sir or Madam:

On behalf of Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc. ("Teva")¹ hereby submits this Citizen Petition pursuant to 21 C.F.R. §10.30 and sections 505(b) and 505(s) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. §355(b), (s). For the reasons that follow, Teva respectfully requests that the Commissioner of Food and Drugs refrain from approving any new drug for the treatment of multiple sclerosis ("MS"), including relapsing-remitting multiple sclerosis ("RRMS"), unless and until the Food and Drug Administration ("FDA") has referred the new drug product to, and considered the recommendations of, the appropriate expert advisory committee, which in this case is the Peripheral and Central Nervous System Advisory Committee ("PCNS Advisory Committee").

I. Actions Requested

Teva is committed to and supports the development of new therapies for the safe and effective treatment of MS, including RRMS. MS is a progressive, highly complex, immune-mediated disorder that affects the central nervous system ("CNS"). Given the complexity of both MS and the human immune system, it is difficult to predict the full range of the clinical effects of a new treatment even after in-depth clinical testing necessary for marketing approval. In recent years, in fact, serious safety issues have been identified with several new treatments for RRMS, including Tysabri (nataluzimab) and Gilenya (fingolimod), after each new drug was

¹ Teva Pharmaceutical Industries Ltd. is a global pharmaceutical company specializing in the development, production, and marketing of generic, proprietary, and branded pharmaceuticals, and active pharmaceutical ingredients. It is among the top 20 pharmaceutical companies and is the leading generic pharmaceutical company in the world. Teva Neuroscience is the branded neurological products subsidiary of Teva Pharmaceutical Industries Ltd. and is responsible for the clinical development, registration, and marketing of Teva's branded neurological products in North America, including Copaxone® (glatiramer acetate).

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approved and made widely available to vulnerable MS patients. The identified risks included rare but serious adverse events, including progressive multifocal leukoencephalopathy (“PML”) and cardiac events. In light of this history, Teva believes that before FDA approves any new molecular entity for the treatment of MS, including RRMS, it is especially important for the Agency to ensure that the risks and benefits of the drug are thoroughly evaluated and that appropriate safeguards are implemented to maintain an acceptable risk-benefit profile.

Accordingly, Teva respectfully requests that the Commissioner refrain from approving any full New Drug Application (“NDA”) or Biologics License Application (“BLA”) for a new drug or biological product for the treatment of MS unless and until the FDA has referred the product to, and considered the recommendations of, the PCNS Advisory Committee.² The FFDCA specifically requires advisory committee review of all new molecular entities prior to approval unless FDA provides sufficient justification for not doing so. 21 U.S.C. § 355(s). In this case, Teva does not believe there is any legitimate reason for refusing to refer new MS drugs to the PCNS Advisory Committee, particularly given the recent history of emerging, serious safety issues with other new treatments for RRMS and the fact that numerous safe and effective treatments for RRMS already are available for patients suffering from the disease. The justification for Teva’s request is set forth in more detail below.

II. Statement of Grounds

A. MS Is A Highly Complex, Immune-Mediated Disorder That Is Progressive and Irreversible

MS is a progressive, highly complex, immune-mediated disorder that affects the CNS. Most experts believe MS is an autoimmune disease in which inflammatory cells attack myelin, a fatty tissue that surrounds and protects nerve axons in the brain, spinal cord, and optic nerves. Myelin enhances the rate of electrochemical signal conduction in the CNS. As myelin and the nerve fibers it protects are damaged or destroyed, the ability of the nerves to conduct electrical impulses to and from the brain is disrupted.^{3,4}

Myelin destruction involves several cell types, with extensive research indicating that subpopulations of antigen-specific T lymphocytes orchestrate a variety of pathogenic mechanisms.^{5,6} Myelin sheaths contain a number of proteins, including myelin basic protein

² Because Teva’s request is limited to full NDAs and BLAs, this Petition is not subject to section 505(q) of the FFDCA, 21 U.S.C. § 355(q). References throughout this Petition to “new drugs” are intended to refer to drugs and biological products that are subject to a full NDA or BLA, not a 505(b)(2) application or Abbreviated New Drug Application.

³ Bjartmar C, Fox RJ. Pathological mechanisms and disease progression of multiple sclerosis: Therapeutic implications. *Drugs Today* 2002;38(1):17-29.

⁴ Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000;343:938-52.

⁵ (Noseworthy et al, 2000; Bjartmar & Fox, 2002)

⁶ O’Connor KC, Bar-Or A, Hafler DA. The neuroimmunology of multiple sclerosis: Possible roles of T and B lymphocytes in immunopathogenesis. *J Clin Immunol* 2001;21:81-92.

("MBP"), proteolipid protein ("PLP"), myelin oligodendrocyte glycoprotein ("MOG"), myelin oligodendrocyte basic protein ("MOBP"), and oligodendrocyte specific protein ("OSP").⁷ These proteins are thought to be the primary self-antigen targets of autoimmune T cells in MS.

MS likely has a genetic component, as evidenced by its strong genetic association with the human leukocyte antigen ("HLA") class II haplotype, HLA-DR.⁸ Alleles of the DR2 haplotype (e.g., DRB1*1501-DQB1*0602) are associated with susceptibility to MS.⁹ HLA-DR plays a critical role in binding antigens and presenting them to T cells for recognition of self, non-self, or danger. The etiology of MS remains unclear; one hypothesis is that MS initiates after a precipitating event such as viral infection, which triggers an immune response capable of promoting cross-reactive autoimmune responses that target a protein or proteins of the myelin sheath.^{10,11}

Indeed, evidence suggests that myelin protein antigens are integral to the immune response in MS. MBP-associated peptides are loaded into the cleft of the HLA-DR molecules on antigen presenting cells ("APCs"), including dendritic cells, macrophages, and monocytes. When APCs are activated, there is an increase in cell surface expression of costimulatory molecules. In turn, the interaction of these costimulatory molecules with the T cell stimulates an antigen-specific T cell response in the periphery. APCs bound with antigenic peptides secrete proinflammatory cytokines, including interleukin-12 ("IL-12") and interleukin-23 ("IL-23"), which promote the differentiation of naive T cells into T-helper type 1 ("Th1") and T-helper type 17 ("Th17") cells, which have been proposed as major cell types for promoting chronic inflammation and autoimmunity.^{12,13,14,15} These T-cell subsets proliferate and secrete pro-inflammatory cytokines, including interferon gamma ("IFN- γ ") and tumor necrosis factor ("TNF").^{16,17} Compared with control subjects, untreated MS patients manifest significantly

⁷ Tzakos AG, Troganis A, Theodorou V, et al. Structure and function of the myelin proteins : Current status and perspectives in relation to multiple sclerosis. *Curr Medicinal Chem* 2005; 12: 1269-87.

⁸ (O'Connor et al, 2001.)

⁹ Barcellos LF, Sawcer S, Ramsay PP, et al. Heterogeneity at the LLA-DRB1 locus and risk for multiple sclerosis. *Hum Mol Genet* 2006; 15: 2813-24.

¹⁰ Lunemann JD, Jelcic I, Roberts S, et al. EBNA1-specific T cells from patients with multiple sclerosis cross react with myelin antigens and co-produce IFN- γ and IL-2. *J Exp Med* 2008; 205: 1763-73.

¹¹ Bogdanos D-P, Smith H, Ma Y, et al. A study of molecular mimicry and immunological cross-reactivity between hepatitis B surface antigen and myelin mimics. *Clin Dev Immunol* 2005; 12: 217-24.

¹² Korn T, Oukka M, Kuchroo V, et al. Th17 cells: Effector T cells with inflammatory properties. *Sem Immunol* 2007; 19: 362-71.

¹³ Kebir H, Ifergan I, Alvarez JI, et al. Preferential recruitment of interferon- γ -expressing T_H17 cells in multiple sclerosis. *Ann Neurol* 2009; 66: 390-402.

¹⁴ Gran B, Zhang GX, Rostami A. Role of the IL-12/IL-23 system in the regulation of T-cell responses in central nervous system inflammatory demyelination. *Crit Rev Immunol* 2004; 24(2): 111-28.

¹⁵ Vaknin-Dembinsky A, Murugaiyan G, Hafler DA, et al. Increased IL-23 secretion and altered chemokine production by dendritic cells upon CD46 activation in patients with multiple sclerosis. *J Neuroimmunol* 2008; 195(1-2): 140-45.

¹⁶ Dhib-Jalbut S. Glatiramer acetate (Copaxone[®]) therapy for multiple sclerosis. *Pharmacol Ther* 2003; 98: 245-55.

greater frequencies of Th1 and Th17 cells that react with one or more myelin proteins in the CNS.^{18,19,20}

Activated antigen-specific T cells can migrate from the periphery into the CNS through the disrupted blood brain barrier. Immune cells in active lesions in the CNS secrete inflammatory cytokines that further enhance the proliferation of Th1 and Th17 cells.²¹ If these antigen-specific Th1 and Th17 cells are cross-reactive with myelin peptides presented by major histocompatibility complex (“MHC”) class II molecules on APCs, including resident microglial cells, then the activated T cells can be further stimulated by myelin proteins within the CNS.^{22,23} This cross-reactivity may initiate and maintain inflammation, causing destruction of the myelin sheath. The cross-reactive T cells may initially react to a single epitope on a myelin protein, but the immune response can spread to additional myelin proteins or different epitopes on the same protein (a phenomenon known as “epitope spreading”), further enhancing inflammation.^{24,25}

In contrast, when an APC presents an antigenic peptide fragment in a noninflammatory environment that lacks IL-12 and IL-23, the activated T cells secrete the generally anti-inflammatory cytokines IL-4, IL-5, IL-10 and IL-13.²⁶ These activated T cells are known as a T-helper type 2 (“Th2”) cells. While MS exacerbations correlate with increased myelin-specific T cells of the Th1 and Th17 phenotypes in the lesion milieu, remissions are associated with higher levels of antigen-specific Th2 and regulatory T cells.^{27,28}

¹⁷ Bettelli E, Korn T, Kuchroo VL. Th17: The third member of the effector T cell trilogy. *Curr Opin Immunol* 2007; 19: 652-57.

¹⁸ Correale J, Farez M. Monocyte-derived dendritic cells in multiple sclerosis: the effect of bacterial infection. *J Neuroimmunol* 2007; 190: 177-89. Correale et al., 1995; Holmoy and Hestvik, 2008; Kim et al., 2002).

¹⁹ Correale J, Gilmore W, McMillan M, et al. Patterns of cytokine secretion by autoreactive proteolipid protein-specific T cell clones during the course of multiple sclerosis. *J Immunol* 1995; 154: 2959-68.

²⁰ (Kebir et al, 2009.)

²¹ Ifergan I, Kebir H, Bernard M, et al. The blood-brain barrier induces differentiation of migrating monocytes into Th17 polarizing dendritic cells. *Brain* 2008; 131: 785-99.

²² Boucher A, Desforages M, Duquette P, et al. Long-term coronavirus-myelin cross-reactive T-cell clones derived from multiple sclerosis patients. *Clin Immunol* 2007; 123: 258-67.

²³ (Bogdanos et al, 2005; Lunemann et al, 2008.)

²⁴ (Bjartmar & Fox, 2002.)

²⁵ Tuohy VK, Yu M, Yin L, et al. Spontaneous regression of primary autoreactivity during chronic progression of experimental autoimmune encephalomyelitis and multiple sclerosis. *J Exp Med* 1999; 189: 1033-42.

²⁶ (Dhib-Jalbut S. 2003.)

²⁷ Venken K, Hellings N, Broekmans T, et al. Natural naive CD4+CD25+CD127^{low} regulatory T cell (Treg) development and function are disturbed in multiple sclerosis patients: Recovery of memory Treg homeostasis during disease progression. *J Immunol* 2008; 180: 6411-20.

²⁸ (Correale et al, 1995.)

Humoral immune responses are also implicated in the pathogenesis of MS. B cells appear to be active participants in the creation and maintenance of myelin lesions in the CNS.²⁹ Activated B cells produce auto-antibodies to myelin proteins that mediate and promote demyelination. In addition, B cells secrete proinflammatory cytokines that stimulate further B cell proliferation and that also stimulate auto-reactive T cells implicated in demyelination, leading to axonal loss and neurodegeneration.³⁰

While myelin degradation is common to all manifestations of MS, there are different clinical courses of the disease. The most common form is RRMS, which afflicts approximately 85% of all MS patients.³¹ People with this form of MS experience acute attacks (also called relapses or exacerbations) of neurological dysfunction that can last days or weeks. Following these attacks, patients experience remission periods during which symptoms may decrease or disappear before recurring.

Early symptoms of MS include sensory disturbances, weakness, generalized fatigue, visual blurring, and dizziness.³² Cognitive impairment, depression, vertigo, sensory loss, sexual dysfunction, pain, and spasticity can develop. As MS progresses, symptoms worsen and neurological disability increases; 50% of patients are unable to walk unassisted within 10 to 15 years of an RRMS diagnosis, and after 25 years, 50% are wheelchair-bound.³³

B. Several New MS Treatments Are Associated With Serious Safety Risks That Were Identified Only After Approval and Widespread Use in MS Patients

Given the complexity of MS as an autoimmune disease, the safety and effectiveness of any new treatment may be unpredictable. This risk is particularly acute for drug products that are intended to interact with a patient's immune system, i.e., immunomodulators. An MS drug that is effective in clinical trials nevertheless may affect a patient's immune system in a way that causes rare but serious side effects, including, for example, PML, Kaposi's sarcoma ("KS"), and an increased risk of serious infections, malignancies, renal damage, and cardiovascular events. Moreover, due to the nature of MS and the immune system, these risks may not develop for months or years and, once apparent, may be irreversible. Accordingly, clinical testing conducted prior to approval, which often is of a limited duration and conducted in a narrow patient population, may not be capable of detecting serious risks associated with MS treatments under conditions of actual use. In sum, although there have been admirable advances in the understanding and treatment of MS in recent years, the unexpected complications that have

²⁹ Nikbin B, Mohyeddin Bonab M, Khosravi F, et al. Role of B cells in the pathogenesis of multiple sclerosis. *Int Rev Neurobiol* 2007; 79: 13-42.

³⁰ (Nikbin et al, 2007.)

³¹ National Multiple Sclerosis Society: Just the facts. 2007-2008. Available at: <http://www.nationalmssociety.org/about-multiple-sclerosis/FAQs-about-MS/index.aspx#howmany>. Accessed October 26, 2009.

³² (Noseworthy et al, 2000.)

³³ Weinshenker BG. The Natural History of Multiple sclerosis. *Mult Scler* 1995; 13: 119-44.

arisen with some recently approved new drugs counsels for caution on the part of FDA before approving new treatments for MS.

In particular, serious safety issues have been identified in recent years with several new treatments for RRMS, including Tysabri (nataluzimab) and Gilenya (fingolimod), *after* the new drugs were approved and made widely available to vulnerable MS patients. For example, Tysabri was approved in 2004 as a first line treatment to reduce the frequency of clinical exacerbations in patients with relapsing forms of MS. FDA considered the drug product to be “an innovative treatment that represents a new approach to treating patients with relapsing forms of multiple sclerosis (MS).”³⁴

A few months after approval, however, Biogen Idec (“Biogen”) voluntarily withdrew Tysabri from the market and suspended dosing in all ongoing clinical trials because of reports of two cases of PML in patients receiving Tysabri, one of which was fatal.³⁵ PML is a rare, serious, progressive viral infection in the brain that usually occurs in immunosuppressed patients and often results in irreversible neurological deterioration and death. There is no known effective treatment for PML. Through January 2012, over 200 cases of PML have been reported in patients treated with Tysabri worldwide and, for some patients, the risk of PML has been estimated to be as high as 11/1,000.³⁶

In June 2006, FDA approved a supplemental application to permit Biogen to resume the marketing of Tysabri under a special restricted distribution program. Significantly, before allowing Tysabri back on the market, FDA sought the expert advice of the PCNS Advisory Committee in order to “decrease the possibility of patients developing PML in the future”³⁷ The PCNS Advisory Committee “recommended a risk-minimization program with mandatory patient registration and periodic follow-up to identify as early as possible any cases of PML that may occur, and to try to determine the reason the infection occurs.”³⁸ As a result of FDA’s re-analysis of the available clinical data and the advice provided by the PCNS Advisory Committee, Tysabri currently is recommended only for second-line therapy “for patients who have had an inadequate response to, or are unable to tolerate, an alternate multiple sclerosis therapy.”³⁹ Moreover, Tysabri is subject to strict distribution and use restrictions under an approved Risk Evaluation and Mitigation Strategy (“REMS”) called the TOUCH™ program, and a boxed warning regarding the risks of PML was added to Tysabri’s approved labeling.

Likewise, serious safety concerns were identified with respect to another MS drug product, Gilenya (fingolimod), after its approval in 2010. Gilenya was approved as the first oral

³⁴ FDA Public Health Advisory on Tysabri (Feb. 28, 2005) (Exhibit 1).

³⁵ *Id.* FDA ultimately imposed a clinical hold on investigations involving Tysabri, which was lifted in 2006.

³⁶ FDA Safety Announcement regarding Tysabri (Jan. 20, 2012) (Exhibit 2).

³⁷ FDA News Release (June 5, 2006) (Exhibit 3).

³⁸ *Id.*

³⁹ Tysabri Package Insert, §1.1 (1/2012) (Exhibit 4).

drug indicated to slow the progression of disability and reduce the frequency and severity of symptoms in MS, providing a potential alternative to injectable therapies for MS. A little more than a year after its approval, however, FDA issued a Drug Safety Communication announcing that it had received a report of a patient with MS who died within 24 hours of taking the first dose of Gilenya.⁴⁰ Based upon its evaluation of additional clinical and postmarket data for Gilenya, FDA determined that although the maximum heart rate lowering effect of Gilenya usually occurs within six hours, the maximum effect could occur as late as twenty hours after the first dose in some patients. Accordingly, Gilenya is now contraindicated in patients with certain pre-existing or recent heart conditions (e.g., myocardial infarction, unstable angina) or stroke or who are taking certain antiarrhythmic medications.⁴¹ In addition, the FDA-approved labeling now recommends enhanced cardiovascular monitoring of patients for at least six hours after the first dose and, for certain high-risk patients (e.g., ischemic heart disease), extended monitoring past six hours.⁴² Although Gilenya was referred to an advisory committee prior to approval, this just underscores the complex and unpredictable safety concerns associated with MS drugs.

In addition to Tysabri and Gilenya, Teva is aware of at least one investigational MS drug currently under FDA review that may be associated with other serious safety risks. In particular, Biogen recently posted some troubling information about the safety and effectiveness of Panoplin (dimethyl fumarate) capsules, also known as BG-12, on a publicly accessible website.⁴³ In addition to constituting unlawful, pre-approval promotion of an unapproved drug product, the website contained animal toxicology data suggesting that dimethyl fumarate (“DMF”), the active ingredient in BG-12, may carry potential risks for renal adverse events. The website stated:

Kidney changes were observed after repeated oral administration of dimethyl fumarate in mice, rats, dogs, and monkeys. Renal tubule epithelia regeneration, suggestive of tubule epithelial injury, was observed in all species. Renal tubular hyperplasia was observed in rats with life time dosing (2 year study). Cortical atrophy was observed in dogs and monkeys, and in monkeys, single cell necrosis and interstitial fibroses were observed in animals that received daily oral doses of dimethyl fumarate for 12 months at six times the RHD based on AUC.⁴⁴

Although the website also stated that “[t]he relevance of these findings to humans is not known[,]” the fact that renal toxicity was seen across all species studied is concerning and suggests that there is a substantial probability the risk is applicable to humans as well. Indeed, this potential risk for renal adverse events was closely monitored in the two recently completed

⁴⁰ FDA Drug Safety Communication regarding Gilenya (fingolimod) (Dec. 20, 2011) (Exhibit 5).

⁴¹ Gilenya Package Insert, § 4 (5/2012) (Exhibit 6).

⁴² Gilenya Package Insert § 2 (5/2012) (Exhibit 6).

⁴³ Panoplin Website Screenshots (Exhibit 7) (accessed December 6, 2012). The website for Panoplin is active and publicly available at <http://warden.7te.net/index.html>. Although it was revised in mid-December to refer to “Product X,” it currently contains detailed product information about Panoplin as a “new” and “approved” oral MS medicine in direct contravention of FDA’s pre-approval promotion restrictions.

⁴⁴ Panoplin Website Screenshots (Exhibit 7).

2-year studies with BG-12 (Gold et al NEJM 2012, and Fox et al NEJM 2012). While substantial incidence of renal adverse events (22% in BG-12 BID) and proteinuria (9% in BG-12 BID), when compared to placebo, have been described as a percent of patients experiencing them, their severity or their sequelae were not reported, thus long term negative outcomes of such high incidence of renal adverse events cannot be ruled out. Although previous clinical trials of Fumaderm, a drug product marketed in Germany that contains DMF as an active ingredient (along with other active ingredients), have not yet specifically identified significant renal problems, they were typically short in duration, and the comparison of toxicity between Fumaderm and BG-12 is complicated by differences in metabolism, disease state, and pharmacological differences.⁴⁵

C. Because of the Serious and Unpredictable Risks Associated With MS Drugs, FDA Should Not Approve Any New Drug for the Treatment of MS Unless and Until It Has Been Reviewed By the PCNS Advisory Committee

In light of the emerging and potential serious safety concerns described above with respect to recently approved and investigational MS drugs, including the risks of PML, KS, cardiac adverse events, increased malignancies, and renal toxicity, FDA should seek advice from the PCNS Advisory Committee before approving any new molecular entity intended to treat MS. This type of expert review is necessary *before approval* to determine whether the risks associated with a new MS drug outweigh its benefits and, if so, whether any risk management strategies (including new warning or cautions or other labeling) should be implemented to achieve an acceptable risk-benefit profile before the new drug product is commercially marketed. Indeed, the PCNS Advisory Committee was instrumental in assessing the risks of, and establishing distribution and use restrictions for, Tysabri (natalizumab) following reports that the drug product was associated with cases of PML. FDA consulted the PCNS Advisory Committee in that case specifically to “decrease the possibility of patients developing PML in the future . . .”⁴⁶

The need for a preapproval advisory committee meeting is particularly acute for new drugs products containing active ingredients that have not previously been approved in the United States. Although FDA generally has discretion whether to refer an application to an advisory committee, in the case of new molecular entities, Congress has significantly circumscribed that discretion. In particular, pursuant to section 505(s) of the FFDCA, 21 U.S.C. § 355(s), Congress has instructed FDA to refer *all* new molecular entities to an advisory committee “[p]rior to approval.” Although the statute permits FDA to circumvent this requirement if there are good reasons for doing so, the Agency is required to document “the

⁴⁵ Recent scientific evidence also suggests that DMF may be associated with PML and KS. In clinical trials, BG-12 therapy resulted in substantial declines in white blood cell and lymphocyte counts, and grade 3 or higher lymphopenia (lymphocyte counts of less than 0.5×10^9 per liter) was seen in between 4% and 5% of patients in the BG-12 groups versus less than 1% in the placebo groups. Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis, New England Journal of Medicine, 367:12, pp. 1087-1097 (Sept. 20, 2012); Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis, New England Journal of Medicine, 367:12, pp. 1098-1107 (Sept. 20, 2012). Although there were no reported cases of PML or KS in the pivotal clinical trials for BG-12, at least three cases of PML and one case of KS have been reported in patients treated with Fumaderm.

⁴⁶ FDA News Release (June 5, 2006) (Exhibit 3).

reasons why the [FDA] did not refer the drug to an advisory committee prior to approval.” 21 U.S.C. § 355(s)(2). In other words, the statute establishes a strong baseline presumption that FDA must refer all new molecular entities to an advisory committee prior to approval, a presumption that can be overcome only if FDA identifies and describes compelling reasons not to make such a referral.⁴⁷

In the case of new MS drugs, there are no reasons, compelling or otherwise, that would justify deviating from the baseline presumption that FDA should refer all new molecular entities to an advisory committee. First, as discussed above, a significant proportion of newly approved MS drugs have been associated with significant safety concerns following approval. The importance of potential safety risks are heightened when drugs of this class are used in combination with other immunosuppressant drugs in the clinical trial setting and in clinical practice. Because many of these emerging risks are rare but extremely serious, such as PML and KS, the PCNS Advisory Committee would be well-situated to assess these risks and to provide expert advice to FDA on the overall risk-benefit profile of a new MS drug, including the need for risk management programs to ensure the safety of the drug as it is introduced to a wider patient population in the United States for the first time. Indeed, the primary reason Congress requires advisory committee review for new molecular entities is to ensure that the risks of new molecules, including rare but serious risks, are thoroughly assessed *before* the new product is made widely available to patients.

Second, because numerous effective treatments for MS currently are available in the United States, there is no pressing scientific or medical justification for approving and facilitating the widespread use of a new MS drug before its safety profile has been thoroughly assessed by an expert advisory panel, as instructed by Congress. Although new oral formulations may have perceived advantages for some patients who are uncomfortable with injectable drug products, it is important to remember that oral MS drugs have been subject to the same emerging safety concerns discussed above as new injectable MS drugs. For example, Gilenya, the first oral MS drug approved in the United States, was determined after approval to be associated with serious cardiovascular risks, prompting FDA to issue a Drug Safety Communication and to require enhanced safety warnings in Gilenya’s approved labeling. The perceived benefits of an oral formulation thus should not be used to justify an approval process that short-circuits the important safeguards established by Congress, including the need for pre-approval advisory committee review.

In sum, because new molecular entities intended for the treatment of MS often entail significant but unpredictable risks, including PML, KS, cardiovascular events and renal toxicity, and because there are no compelling reasons for FDA to skip an otherwise mandatory advisory committee meeting for products in this class, FDA should refer all applications for new molecular entities intended to treat MS to the PCNS Advisory Committee prior to approval. This is consistent not only with 21 U.S.C. § 355(s) but also with good scientific and regulatory practice and the protection of the public health.

⁴⁷ In the past, FDA has refrained from referring a new drug to an FDA advisory committee for a variety of compelling reasons, including where the drug “did not raise significant safety or efficacy issues that were unexpected in a drug of this class.” See, e.g., Approval Letter for Prepopik (July 16, 2012), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202535Orig1s000Approv.pdf.

D. Conclusion

For the foregoing reasons, Teva respectfully requests that the Commissioner refrain from approving any new MS treatment unless and until it holds a meeting, and thoroughly considers the recommendations, of the PCNS Advisory Committee regarding the risk-benefit profile of the new drug and any risk mitigation strategies necessary for approval.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31(a).

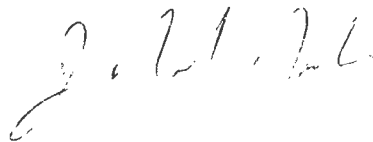
IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

V. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "J. Michael Nicholas", is written over a horizontal line.

J. Michael Nicholas, Ph.D.,
Sr. Director

cc: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

Ellis Unger, M.D.
Director, Office of Drug Evaluation I

Russell G. Katz, M.D.
Director, Division of Neurology Products