DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 2 7 2013

J. Michael Nicholas, Ph.D.
Teva Pharmaceutical Industries Ltd.
901 E. 104th Street, Suite 900
Kansas City, MO 64131

Re: Docket No. FDA-2013-P-0025

Dear Dr. Nicholas:

This letter responds to the above-referenced citizen petition (Petition) submitted to the Food and Drug Administration (FDA or the Agency) by Teva Neuroscience, Inc., on behalf of Teva Pharmaceutical Industries Ltd. (collectively referred to as Teva), dated December 31, 2012. Your Petition requests that FDA refrain from approving any full new drug application (NDA) or biologics license application (BLA) for a new drug or biological product[1] for the treatment of multiple sclerosis (MS), including relapsing-remitting multiple sclerosis (RRMS), unless and until FDA has referred the new drug to, and considered the recommendations of, an advisory committee (Petition at 2).[2] The advisory committee that generally reviews drugs for the treatment of MS is the Peripheral and Central Nervous System Drugs (PCNSD) Advisory Committee.

We have carefully considered the information submitted in the Petition. For the reasons described below, your request is denied.

I. BACKGROUND

A. Legal and Regulatory Background

Part of FDA's mission is to protect the public health by assuring the safety, effectiveness, and security of human drug products. FDA may call upon experts outside of the Agency for advice on complex medical, scientific, and policy issues. This includes questions related to the development and evaluation of drugs regulated by FDA. One way that FDA can access external experts is by convening an advisory committee. An advisory committee allows FDA to benefit from the advice of outside experts while providing a

[1] For the purposes of this response, all references to "drug" and "drugs" include both human drug products and biological products.

[2] Noting your reference to full NDAs on p. 2 of the Petition and your general focus on new active moieties (as discussed in footnote 5), we interpret your request as pertaining to drugs containing new active moieties intended for the treatment of MS. Because we are denying your request with respect to this class, we would also deny this request if it were interpreted more broadly as pertaining to all "new drugs" (as defined in section 201(p) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 321(p)) and biological products for the treatment of MS.

forum for public discussion of important and potentially controversial issues. However, the advisory committee's recommendations are purely advisory and do not bind or otherwise obligate the Agency.[3]

In most instances, FDA has discretion to consider whether to refer a matter to an advisory committee for input.[4] The Agency's discretion is reflected in section 505(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which states that:

> Prior to the approval of a drug no active ingredient (including any ester or salt of the active ingredient) [5] of which has been approved in any other application under this section or section 262 of title 42, [FDA] shall—
>
> (1) refer such drug to [an FDA] advisory committee for review at a meeting of such advisory committee; or
>
> (2) if [FDA] does not refer such a drug to [an FDA] advisory committee prior to the approval of the drug, provide in the action letter on the application for the drug a summary of the reasons why [FDA] did not refer the drug to an advisory committee prior to approval.[6]

In August 2008, FDA issued draft guidance describing factors the Agency proposes to consider in determining whether a matter should be referred to an advisory committee.[7] These factors include whether the matter: (1) is of such significant public interest that it would be highly beneficial to obtain the advice of an advisory committee, (2) is so controversial that it would be highly beneficial to obtain the advice of an advisory committee, or (3) requires a special type of expertise that an advisory committee could provide.[8] The draft guidance proposes that if one or more of these factors are met, then "the matter at issue should generally be referred to an advisory committee."[9] The draft guidance also proposes that if none of the factors is present, then an advisory committee

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[3] The Federal Advisory Committee Act provides that the function of advisory committees is advisory only, and that all matters under an advisory committee's consideration should be determined by the agency. See 5 U.S.C. Appendix 2, section 2(b)(6). See also 21 C.F.R. 14.5(b).

[4] 21 C.F.R. 14.5(a) (1). By contrast, FDA must refer some matters to advisory committees in certain circumstances. See, e.g., sections 505A(i)(2)(A), 513(c), and 520(l)(2) of the FD&C Act (21 U.S.C. 355a(i)(2)(A), 360c(c), and 360j(l)(2)).

[5] Noting your reference to "new molecular entity" throughout the Petition to suggest an active ingredient (including any ester or salt of the active ingredient) that has not been approved in any other NDA or BLA, we use "new active moiety" instead of new molecular entity. See 21 C.F.R. 314.108, 316.3.

[6] 21 U.S.C. 355(s).

[7] See generally, FDA draft guidance, *Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings*, August 2008, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125651.pdf. When final, this guidance will represent FDA's current thinking on this topic.

[8] Id.

[9] Id.

should not be convened, so that resources are devoted to "matters in which the Agency would most benefit from the advice of outside experts."[10]

B. MS Drug Products

MS is a chronic autoimmune disease of the central nervous system that disrupts communication between the brain and other parts of the body.[11] MS is caused by damage to the myelin sheath, which is a protective covering surrounding nerve cells. When the myelin sheath is damaged, nerve signals slow down or stop. The nerve damage is caused by inflammation occurring when the body's own immune system attacks the nervous system.[12] For most people with MS, episodes of worsening function (relapses) are initially followed by recovery periods (remissions). Over time, recovery periods may be incomplete, leading to progressive decline in function and increased disability. Symptoms vary among patients because the location and severity of each attack may be different. Patients with MS often experience muscle weakness, difficulty with coordination and balance, and fatigue.[13]

Currently, there is no known cure for MS.[14] FDA has approved several therapies that may slow the progression of MS and control its symptoms. In your Petition, you highlight two products that FDA has approved for the treatment of MS: Tysabri (natalizumab) injection (BLA 125-104) and Gilenya (fingolimod) capsules (NDA 22-527) (Petition at 5-7).[15] Your Petition includes a description of safety concerns that emerged after these products were approved and used in clinical practice.

FDA approved Tysabri on November 23, 2004, for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations. In February 2005, its sponsor, Biogen Idec Inc. (Biogen), voluntarily suspended marketing of Tysabri due to cases of progressive multifocal leukoencephalopathy (PML).[16] FDA also issued a clinical hold on all trials with Tysabri in February 2005. In March 2006, before Tysabri was reintroduced to the market, FDA sought the advice of the PCNSD Advisory

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[10] Id.

[11] National Institutes of Health, National Library of Medicine, A.D.A.M. Medical Encyclopedia, Multiple sclerosis, available at http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001747/.

[12] Id.

[13] Id.

[14] Id.

[15] Other MS drugs approved by FDA, include, but are not limited to: Copaxone (glatiramer acetate) injection, which is marketed by Teva, and Avonex (interferon beta-1a) injection.

[16] See FDA Public Health Advisory - Suspended Marketing of Tysabri (natalizumab), Feb. 28, 2005, available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051761.htm.

Committee.[17] In June 2006, Biogen resumed marketing of Tysabri with a Risk Minimization Action Plan (RiskMAP),[18] called Tysabri Outreach: Unified Commitment to Health (TOUCH) program, to minimize the risk of PML.[19] Currently, Tysabri is approved as monotherapy for the treatment of relapsing forms of MS to delay accumulation of physical disability and reduce the frequency of clinical exacerbations.[20] Tysabri is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternative MS therapy.

FDA approved Gilenya on September 21, 2010, for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.[21] In December 2011, FDA announced a report of a patient with MS who had died within 24 hours of taking the first dose of Gilenya.[22] FDA determined that the maximum heart-rate- lowering effect of Gilenya typically occurs within 6 hours, though it could occur as late as 20 hours after the first dose in some patients.[23] Accordingly, Gilenya is now contraindicated in patients with certain preexisting or recent heart conditions or stroke or who are taking certain antiarrhythmic medications and enhanced cardiovascular monitoring is now recommended.[24]

Your Petition also discusses alleged safety concerns associated with an investigational drug product intended to treat MS, dimethyl fumarate capsules (Petition at 7-8). You state that animal toxicology data suggest that dimethyl fumarate may carry potential risks for renal toxicity (Petition at 7). You also cite to two publications involving studies with dimethyl fumarate. You suggest that these studies show that dimethyl fumarate may be

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[17] See generally, transcript of March 7-8, 2006, meeting of FDA's Peripheral and Central Nervous System Drugs Advisory Committee, available at http://www.fda.gov/ohrms/dockets/ac/cder06.html#PeripheralCentralNervousSystem.

[18] See FDA News Release, FDA Approves Resumed Marketing of Tysabri Under a Special Distribution Program, June 5, 2006, available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108662.htm.

[19] See Tysabri Risk Minimization Action Plan: Summary of TOUCH, available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM107197.pdf. The RiskMAP was converted to a Risk Evaluation and Mitigation Strategy (REMS) in October 2011. 73 FR 16313-16314 (Mar. 27, 2008). Tysabri was included in the list of drug products deemed to have in effect an approved REMS under section 505-1 of the FD&C Act (21 U.S.C. 355-1) with the passage of the FDA Amendments Act (FDAAA) of 2007.

[20] Tysabri (natalizumab) package insert.

[21] Gilenya (fingolimod) package insert.

[22] FDA Drug Safety Communication: Safety review of a reported death after the first dose of multiple sclerosis drug Gilenya (fingolimod), Dec. 20, 2011, available at http://www.fda.gov/Drugs/DrugSafety/ucm284240.htm.

[23] FDA Drug Safety Communication: Revised recommendations for cardiovascular monitoring and use of multiple sclerosis drug Gilenya (fingolimod), May 14, 2012, available at http://www.fda.gov/Drugs/DrugSafety/ucm303192.htm.

[24] Id.

associated with high incidences of renal adverse events and may have long-term negative outcomes (Petition at 8). Although FDA does not comment on investigational products, as discussed in section II.C., the Agency has approved this product today without referring it to an advisory committee.

II. DISCUSSION

A. There is No Presumption that FDA Will Refer All Products with a New Active Moiety to an Advisory Committee

You acknowledge that FDA has discretion to refer an NDA or BLA to an advisory committee prior to acting on the application; however, for new active moieties, you maintain that Congress has "circumscribed that discretion" (Petition at 8). You claim that under section 505(s) of the FD&C Act, Congress has instructed FDA to refer all new active moieties to an advisory committee prior to approval, unless there are "good reasons" for "circumventing" this requirement (Petition at 8). You state that section 505(s) of the FD&C Act "establishes a strong baseline presumption that FDA must refer all new active moieties 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" (Petition at 9).

We disagree with your interpretation of the statute. Congress has not, as you suggest, established a requirement or presumption that drugs containing a new active moiety will be referred to an advisory committee. Rather, Congress mandated in section 505(s) of the FD&C Act that FDA consider whether or not advisory committee review is necessary prior to the approval of such products, and if FDA concludes that it is not necessary, FDA must provide a summary of the reasons for not referring the product to an advisory committee in the action letter for the NDA or BLA. The law vests the Agency with discretion to determine on a case-by-case basis whether to seek advisory committee review prior to taking action on an application for a new active moiety.

Further, there is no requirement that FDA provide "compelling reasons" or "sufficient justification" for not making a referral to an advisory committee. You have suggested a standard that is different from what is required by law. The plain language of the statute mandates that FDA provide in the action letter for the NDA "a summary of the reasons" why the drug was not referred to an advisory committee prior to approval.

B. FDA Has Exercised its Discretion Appropriately

You also claim that given the complexity of MS, the safety and effectiveness of any new treatment may be unpredictable, and that clinical testing conducted prior to approval may not be capable of detecting serious risks associated with MS treatments under conditions of use (Petition at 5). Because of these factors, you assert that FDA should seek advice from the PCNSD Advisory Committee before approving any new active moiety intended to treat MS. You maintain that advisory committee review should be required to

determine whether the risks outweigh the new product's benefits and whether any risk management strategies should be implemented before the new drug product is commercially available (Petition at 8-9).

We are denying this requested action. FDA reviews many applications for drugs that target complex diseases like MS, and not all such applications are appropriate for advisory committee review. If the Agency determines, for example, that the special expertise that an advisory committee can provide is not necessary, then an advisory committee is not likely to be convened. Moreover, even if FDA seeks advice from an advisory committee on the benefits and risks of a new product or on risk management strategies, the committee's recommendations are not binding on the Agency.

Additionally, you have not explained how – for all drugs containing new active moieties intended to treat MS – advisory committee review prior to approval will predict or mitigate safety concerns that may emerge after a product is approved. Indeed, you point out the difficulty of predicting post-approval safety concerns by citing the approval history of Gilenya. In that case, even though an advisory committee was convened prior to approval, new safety concerns emerged after Gilenya was marketed (Petition at 7).

Your Petition asks the Agency to determine that in all cases drugs containing new active moieties intended to treat MS must be reviewed by an advisory committee prior to approval. We are not persuaded that the Agency should make such a determination. For the reasons stated above, FDA will not require advisory committee review of all such products. Rather, FDA will use its discretion and determine whether MS products, including those with a new active moiety, should be referred for advisory committee review on a case-by-case basis.

C. Approval of Tecfidera (dimethyl fumarate)

Today, FDA approved Tecfidera (dimethyl fumarate) capsules for the treatment of adults with relapsing forms of MS. Results from two adequate and well-controlled clinical trials showed that subjects taking Tecfidera had fewer MS relapses compared to subjects taking a placebo. Further, one trial showed that subjects taking Tecfidera experienced a worsening of disability less often than subjects taking a placebo.

Data contained in the NDA are naturally more detailed than those included in the published reports cited in the Petition. Although nonclinical data may have suggested the potential for renal toxicity of Tecfidera in humans, the clinical safety database included in the NDA did not identify any significant renal toxicity in humans over a 2-year period. Finally, Tecfidera's sponsor is required to conduct a large 5-year observational study in MS patients, with close monitoring for renal toxicity, as a postmarketing requirement.

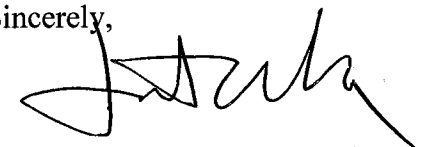
The Agency concluded that the safety profile of Tecfidera is acceptable for the treatment of patients with relapsing forms of MS, and therefore determined, within its discretion, that review by an advisory committee was not necessary prior to the approval of

Tecfidera. Although, as Teva notes, there are several safe and effective treatments for MS currently available in the United States (Petition at 9), FDA considers patient access to a variety of safe and effective treatment options important to public health.

III. CONCLUSION

The law gives FDA discretion to determine whether to refer an application for a new active moiety to an advisory committee, and the Agency has exercised that discretion appropriately here. For the reasons described above, your request is denied.

Sincerely,



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