



Larry Downey
Executive Vice President, US Branded Pharmaceuticals
Teva Pharmaceuticals USA
c/o Teva Neuroscience, Inc.
901 East 104th Street, Suite 900
Kansas City, MO 64131

RE: NDA# 020622
COPAXONE[®] (glatiramer acetate injection) solution for subcutaneous injection
MA #762

WARNING LETTER

Dear Mr. Downey:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed 2011 AAN Professional Exhibit Panels “AAN Static Panels G double” (COP112014807/110193) (2011 AAN Exhibit Panels G) for COPAXONE[®] (glatiramer acetate injection) solution for subcutaneous injection (Copaxone), submitted by Teva Neuroscience, Inc. (Teva) under cover of Form FDA-2253, as well as the “Team COPAXONE[®]” webpage (COP110006303/110312), “David Kyle” webpage (COP100006331/102252), and “Karen Stewart” webpage (COP100006324/102245) for Copaxone.¹

These promotional materials are false or misleading because they overstate the efficacy, present unsubstantiated claims, broaden the indication of Copaxone, omit and minimize important risk information associated with the drug, present unsubstantiated superiority claims, and omit material facts. Thus, the 2011 AAN Professional Exhibit Panels and “Team COPAXONE[®]” webpages misbrand Copaxone in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a), (n); 321(n). See 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (ii), (iv), (xviii) & (e)(7)(i). These violations are concerning from a public health perspective because they suggest that Copaxone is safer or more effective than has been demonstrated by substantial evidence or substantial clinical experience.

¹ “Team COPAXONE[®]” webpage, “David Kyle” webpage, and “Karen Stewart” webpage, at <http://www.sharedsolutions.com/Living-With-MS/TeamCOPAXONE.aspx>, <http://www.sharedsolutions.com/Living-With-MS/TeamCOPAXONE/AboutMe/David-Kyle.aspx>, and <http://www.sharedsolutions.com/Living-With-MS/TeamCOPAXONE/AboutMe/Karen-Stewart.aspx> (last accessed December 6, 2011), respectively.

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Copaxone.² According to its FDA-approved product labeling (PI):

COPAXONE is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

Copaxone is associated with a number of serious risks. According to its PI, Copaxone is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol. In addition, the PI contains Warnings and Precautions regarding immediate post-injection reaction, chest pain, lipoatrophy and skin necrosis, and potential effects on immune response.

The most common adverse reactions ($\geq 10\%$ and ≥ 1.5 times higher than placebo) reported in controlled studies were injection site reactions, vasodilatation, rash, dyspnea, and chest pain.

Overstatement of Efficacy/Unsubstantiated Claims

Promotional materials are misleading if they represent or suggest that a drug is more effective or safer than has been demonstrated by substantial evidence or substantial clinical experience.

The 2011 AAN Exhibit Panels G include claims and presentations such as the following (underlined emphasis added):

- **“20 years of proven safety”**
- **“No other RRMS therapy can demonstrate long-term results like COPAXONE[®]”**

Long-term experience: Results after an average of 22 years with RRMS” in conjunction with the claims, “8 years untreated [with a diagnosis of RRMS since 1983]” and “Up to 15 years continuous COPAXONE[®] therapy (mean 14 years), open label study,” and a graph showing mean EDSS scores over time, from 1991 to 2006.

- **“Expanded Disability Status Scale (EDSS) scores remained stable after an average of 15 years on therapy.”**
- **“OPEN-LABEL FOLLOW-UP—5 YEARS AFTER RANDOMIZATION**
...

² This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.

Early treatment with COPAXONE[®] reduced the risk of CDMS [clinically definite multiple sclerosis] by 41.1% vs delayed treatment over 5 years (P=0.0005).”

These presentations misleadingly overstate the safety and efficacy of Copaxone by implying that the drug has proven long term (e.g. 20 years, 15 years, etc.) safety and efficacy, when this has **not** been demonstrated by substantial evidence or substantial clinical experience. The CLINICAL STUDIES section of the PI only includes data for up to **three years** in duration. The AAN exhibit panels refer to open-label extension studies, i.e., the PreClSe study as well as another pivotal trial for Copaxone, neither of which constitute substantial evidence to support the above claims. Specifically, these studies did not account for any self-selection among the patients who chose to participate in the open-label studies. In addition, it is unclear as to why certain patients dropped out or were lost to follow-up. For example, in one of the open-label studies described above, only 100 patients remained in the study at 15 years out of the original 231 patients. Any conclusions suggested by the extension study would have to be confirmed in adequate and well-controlled clinical studies.

Furthermore, the claim, “No other RRMS therapy can demonstrate long-term results like COPAXONE[®],” misleadingly suggests that Copaxone is superior to other RRMS therapies. FDA is not aware of adequate and well-controlled clinical trials demonstrating that Copaxone is safer, more effective, or otherwise superior to other treatments for RRMS. If you have data to support these claims, please submit them to FDA for review.

Overstatement of Efficacy/Broadening of Indication

Promotional materials are misleading if they suggest that a drug is more effective or useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

The “Team COPAXONE[®]” webpage presents the following claims (underlined emphasis added):

- “**For over ten years** . . . Team COPAXONE[®] has honored the accomplishments of people who refuse to let MS stand in the way of their ambitions. All of our team members have one thing in common: they live the life they’ve dreamed.”
- “If you are passionate and dedicated to actively living your life, and if you don’t let MS get in the way of your dreams, you could be the next member of Team COPAXONE[®].”

In addition, the “David Kyle” and “Karen Stewart” webpages include claims such as the following (underlined emphasis added):

“David Kyle” webpage: “**Running, Swimming and Biking Against Multiple Sclerosis**”

Before Copaxone

- “It’s hard to believe that just a few years ago, this energetic and dynamic athlete

had to use a cane for mobility and often could barely muster enough energy to work half a day. This was the case for David, who was diagnosed with multiple sclerosis (MS) in 2002. David awoke one morning experiencing numbness in his toes.”

- “Over the course of a few weeks, the numbness moved up his body and he eventually became partially paralyzed from the chest down. The symptoms subsided briefly only to return just six months later, this time advancing to his entire right side.”

After Copaxone

- “With the help of his doctor, David began COPAXONE® (glatiramer acetate injection) therapy in 2003”
- “After a year and a half of hard work and determination, David was the USA Triathlon National Champion in the physically challenged category.”
- David went on to compete and win numerous national and international triathlons from 2005-2008.

“Karen Stewart” webpage: “**Taking on Multiple Sclerosis, One Step at a Time**”

Before Copaxone

- “Karen was diagnosed with relapsing-remitting multiple sclerosis (RRMS) in 1996, after experiencing numbness in her leg and optic neuritis, an inflammation of the optic nerve causing an acute loss of vision.”
- “In the years following her diagnosis, Karen’s health began to worsen. She could no longer walk unassisted, fatigue became a daily challenge and, eventually, the worsening of her symptoms forced her to leave her job.”

After Copaxone

- “In 1998, after discussing therapy options with her neurologist, she began taking COPAXONE® . . . to manage her MS.”
- “Although individual results may vary, over the past few years, Karen has made fitness a priority in her life. She exercises six days a week, added Pilates to her exercise regimen and continues to work as a registered nurse (RN). To date, Karen has walked 22 marathons . . .”

The above claims misleadingly broaden the indication and overstate the efficacy of Copaxone by implying that Copaxone reverses patients’ disability and enables them to lead an active lifestyle, return to work, accomplish great athletic feats, and “live the life they’ve

dreamed.” For example, prior to treatment with Copaxone, “Karen Stewart” was constantly feeling fatigue, was not able to walk unassisted, and was forced to leave her job. However, after Copaxone treatment, she returned to work as a nurse and walked 22 marathons. Similarly, “David Kyle” was partially paralyzed and barely had enough energy to work half a day prior to Copaxone. However, after Copaxone, he was able to compete and win many national and international triathlons for the physically challenged.

While these statements may be an accurate reflection of these patients’ experiences, the patient testimonials misleadingly broaden the indication and overstate the efficacy of Copaxone. As described in the Background section, Copaxone has demonstrated efficacy in decreasing the frequency of relapses in patients with RRMS. However, Copaxone is **not** indicated for slowing, preventing or reversing physical disability associated with RRMS. Moreover, FDA is not aware of substantial evidence or substantial clinical experience supporting the implication that Copaxone treatment will result in the magnitude of effects as described in the above patient testimonials. We note that these patient testimonials, in part, state, “[a]lthough individual results may vary” (Karen Stewart webpage) or “[w]hile individual results may vary” (David Kyle webpage). However, these statements do not mitigate the misleading impression that Copaxone can prevent or reverse the physical disability caused by RRMS. The personal experiences of “Team Copaxone” patients such as “David Kyle” and “Karen Stewart,” do not constitute substantial evidence to support such claims and presentations. If you have data to support these claims, please submit them to FDA for review.

In addition, the totality of the presentation broadens the indication for Copaxone by implying that Copaxone is approved to treat **all** types of MS, when this is not the case. As described in the Background section, Copaxone is indicated for **reduction of the frequency of relapses in patients with RRMS**, including patients who have experienced a first clinical episode and have MRI features consistent with MS. However, as detailed above, the webpages make claims that misleadingly broaden the indication for Copaxone, such as, “**Running, Swimming and Biking Against Multiple Sclerosis**” (“David Kyle” webpage) and “**Taking on Multiple Sclerosis, One Step at a Time**” (“Karen Stewart” webpage) (bolded emphasis original; underlined emphasis added). We acknowledge that the webpages do make mention of RRMS diagnoses for David Kyle and Karen Stewart. However, the presentation is not adequate to mitigate the overwhelming implication that Copaxone is approved for the treatment of all types all MS.

Furthermore, the webpages state that Karen Stewart began taking Copaxone in 1998, and David Kyle began Copaxone therapy in 2003. While we acknowledge that Karen Stewart and David Kyle may have begun therapy in 1998 and 2003, respectively, the inclusion of these dates suggests ongoing treatment and implies that Copaxone is effective for reducing the frequency of relapses or exacerbations for a period of time beyond what has been demonstrated by substantial evidence or substantial clinical experience. As previously stated, the CLINICAL STUDIES section of the PI only includes data for up to **three years** in duration. If you have data to support the long-term safety and efficacy of Copaxone, please submit them to FDA for review.

In addition to the “David Kyle” and “Karen Stewart” webpages, we note that the “Team COPAXONE®” website highlights other patients with MS who have been treated with Copaxone and their subsequent athletic accomplishments. The respective webpages of these individual patient profiles are misleading for similar reasons.

The 2011 AAN Exhibit Panels G present the following claims and presentation (emphasis in original):

- “Up to 15 years continuous COPAXONE® therapy (mean 14 years), open label study” in conjunction with a graph showing mean EDSS scores over time (1991-2006) and the claim, “**82% walking independently** (n=100; EDSS < 6)”
- “**Expanded Disability Status Scale (EDSS) scores remained stable after 15 years on therapy.**”

These claims overstate the efficacy of Copaxone by suggesting that 82% of patients on Copaxone were able to walk independently, as demonstrated by mean EDSS scores over 15 years, when this has not been supported by substantial evidence or substantial clinical experience. As stated above, the open-label extension study does not constitute substantial evidence to support the above efficacy claims. Furthermore, the above claims and presentation misleadingly broaden the indication by suggesting that Copaxone prevents the progression of disability. According to the PI, Copaxone is only approved for the reduction of relapses in patients with RRMS, and is **not** approved for slowing the progression of disability of the disease. We acknowledge that there is a statement at the bottom of the exhibit panel which reads, “The labeling for COPAXONE® does not include an indication for slowing progression of disability”; however, this statement does not mitigate the above misleading presentations. As stated above, we are not aware of substantial evidence to support claims that Copaxone prevents the progression of physical disability, or slows the accumulation of disability associated with RRMS.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Promotional materials also are misleading if they fail to include a balanced presentation of information relating to the risks associated with the use of a drug along with the presentation of promotional claims relating to the effectiveness of the drug.

The “Team COPAXONE®” webpage, in addition to the “David Kyle” and “Karen Stewart” webpages are misleading because they include numerous claims regarding the benefits of Copaxone, but fail to include **any** risk information associated with the drug in the body of the webpages. We note that there are links to the “Important Safety Information” and to the full PI on these webpages; however, these links do not mitigate the misleading omission of risk information from the body of each of these webpages. Additionally, other patient testimonials found on “Team COPAXONE®” website, www.sharedsolutions.com/Living-With-MS/TeamCOPAXONE.aspx, are misleading for similar reasons.

Omission and Minimization of Risk Information/Unsubstantiated Superiority Presentation

The 2011 AAN Exhibit Panels G present the claim, “**20 years of proven safety**” (emphasis in original) in conjunction with a table containing two columns, listing only three risks associated with Copaxone and highlighting numerous risks **not** associated with Copaxone. In addition, the following claim is included below the table: “COPAXONE[®] has no warnings or precautions for these serious adverse events.”

The totality of this presentation minimizes the risks associated with Copaxone and misleadingly suggests that Copaxone is safer than has been demonstrated by substantial evidence or substantial clinical experience. Additionally, this presentation misleadingly implies that Copaxone is safer than other treatments for RRMS because Copaxone is not associated with many serious risks that are generally attributed to other RRMS drugs. For example, the table suggests that Copaxone is **not** associated with immunosuppression/infections, decrease in pulmonary function, and anaphylaxis/hypersensitivity, when this is not the case. While we acknowledge that the PI for Copaxone does not have these risks listed in the WARNINGS AND PRECAUTIONS section, it does not mean that such risks are not associated with the drug. According to the ADVERSE REACTIONS section of the PI, infection, influenza, hypersensitivity, and dyspnea were reported in clinical trials for Copaxone at a rate higher than that of the placebo group. In addition, dyspnea, hypersensitivity, and urticaria were among the most common adverse reactions leading to discontinuation of Copaxone. Therefore, it is misleading to imply that Copaxone is not associated with risks such as those mentioned above.

Additionally, this presentation omits material information about other attributes of Copaxone therapy, such as Contraindications, Warnings and other serious risks that are highly relevant to any decision about whether or not to prescribe Copaxone or another treatment for RRMS. Specifically, the table fails to present the Warnings for chest pain, skin necrosis and the potential effects of Copaxone on immune response. Furthermore, it minimizes the serious risk of immediate post-injection reactions by failing to mention, as described in the WARNINGS AND PRECAUTIONS section of the PI, that “[d]uring the postmarketing period, there have been reports of patients with similar symptoms [of immediate post-injection reactions (IPIRs)] who received emergency medical care.” Moreover, this presentation fails to include material information that injection site reactions such as erythema, pain, pruritus, mass, edema, hypersensitivity, fibrosis, and atrophy occurred at a higher rate with Copaxone than with placebo, and that injection site reactions were one of the most common adverse reactions leading to discontinuation of Copaxone. By omitting these important risks, the presentation minimizes the risk of Copaxone and implies that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

In addition, the 2011 AAN Exhibit Panels G include the following claim, “**NO initial or routine monitoring required or recommended**” (emphasis in original) accompanied by a table showing the initial and routine monitoring recommendations for Copaxone, IFN β , natalizumab, and fingolimod along with a column that shows no initial or routine monitoring recommendations for Copaxone.

The totality of this presentation misleadingly suggests that Copaxone is a better and safer treatment option for RRMS than INF β , natalizumab and fingolimod because it is the **only** one that does not require initial or routine monitoring. We note that the monitoring recommendations are consistent with the PIs of INF β , natalizumab and fingolimod. However, without a comparison of other attributes associated with the products, or, potentially other material facts that may be necessary within the context of a comparative presentation, the exhibit panels misleadingly suggest that Copaxone is a safer, better, or otherwise superior treatment option for RRMS. As stated above, FDA is not aware of adequate and well-controlled head-to-head clinical trials demonstrating that Copaxone is safer, more effective than, or otherwise superior to, other RRMS therapies.

Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The 2011 AAN Exhibit Panels G present a Kaplan-Meier graph of the PreCISe study, showing the time to a second clinical event, in conjunction with the claim, “**45% risk reduction**” (emphasis in original). This presentation of the relative risk reduction is misleading because it omits material facts regarding the actual relapse rates for Copaxone and placebo, implying a greater reduction in relapse rates than has been demonstrated. According to the CLINICAL STUDIES section of the PI, “The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were **42.9%** in the placebo group and **24.7%** in the COPAXONE group” (emphasis added).

Conclusion and Requested Action

For reasons discussed above, the 2011 AAN exhibit panels and webpages misbrand Copaxone in violation of the FD&C Act, 21 U.S.C. 352(a), (n); 321(n) See 21 CFR 202.1 (e)(3)(i); (e)(5); (e)(6)(i), (ii), (iv), (xviii) & (e)(7)(i).

OPDP requests that Teva immediately cease the dissemination of violative promotional materials for Copaxone such as those described above. Please submit a written response to this letter on or before March 28, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Copaxone that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional pieces and focus on the corrective messages, OPDP recommends that corrective piece(s) include a description of the violative promotional pieces, include a summary of the violative messages, provide information to correct each of the violative messages, and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, MD 20705-1266**, or by facsimile at 301-847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Promotion (DPP) and the Division of Direct-to-Consumer Promotion (DDTCP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. In all future correspondence regarding this matter, please refer to MA # 762 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Copaxone comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS W ABRAMS
03/14/2012