DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Kevin Hanlon, Manager
Regulatory Affairs, Advertising & Promotion
Merz Pharmaceuticals GmbH
6501 Six Forks Road
Raleigh, NC 27615

RE: BLA 125360
XEOMIN (incobotulinumtoxinA) for injection, for intramuscular or intraglandular use
MA 883

Dear Kevin Hanlon:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, "Xeomin Aesthetic Social Media" (XASM-28) (post) for XEOMIN (incobotulinumtoxinA) for injection, for intramuscular or intraglandular use (Xeomin). The post was made by both Merz Pharmaceuticals GmbH (Merz) on the Xeomin Aesthetics Instagram account and Nate Berkus on his personal Instagram account in "[p]aid partnership with **xeominaesthetic**" (emphasis original).[1] The post makes false or misleading representations and suggestions about the risks and efficacy of Xeomin. Thus, the post misbrands Xeomin within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). 21 CFR 202.1 (e)(5); (e)(7)(viii). These violations are concerning from a public health perspective because the promotional communication creates a misleading impression regarding the safety and effectiveness of Xeomin, a drug with a number of serious and potentially life-threatening risks, including a boxed warning regarding the risk of distant spread of toxin effects.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Xeomin.[2] According to the INDICATIONS AND USAGE section of the FDA-approved Prescribing Information (PI)[3] (in pertinent part):

XEOMIN is indicated for the temporary improvement in the appearance of moderate to

[1] Posted on Nate Berkus's (https://www.instagram.com/nateberkus/reel/C0hIKHqR9xo/) and Xeomin Aesthetics's (https://www.instagram.com/reel/C0hIKHqR9xo/?igsh=Z3g1cmQzN2IwdzYy) verified Instagram accounts. Last accessed October 28, 2024.
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional communication cited in this letter.
[3] The version of the Xeomin PI referred to in this letter is dated September 2023.

severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

The PI for Xeomin contains a boxed warning regarding the distant spread of toxin effect. Xeomin is contraindicated in patients with a known hypersensitivity to any botulinum toxin product or to any components of Xeomin and in patients with an infection at the proposed injection site. In addition, the PI for Xeomin includes warnings and precautions regarding the lack of interchangeability between botulinum toxin products, hypersensitivity reactions, dysphagia and breathing difficulties, corneal exposure, corneal ulceration, and ectropion in patients treated for blepharospasm, risk of ptosis in patients treated for glabellar lines, human albumin and transmission of viral diseases and pre-existing conditions at the injection site. The most common adverse reaction reported with Xeomin for the treatment of glabellar lines was headache.

Prior Communication(s)

OPDP notes that our advisory comments dated September 17, 2010, and January 11, 2012, to Merz addressed (b) (4) [redacted]. We are concerned that Merz is not presenting the benefits and serious risks of the drug in a truthful and non-misleading manner, despite concerns previously expressed by OPDP.

False or Misleading Risk Presentation

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to risk. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts 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 promotional communication.

This post is misleading because it fails to present information relating to side effects and contraindications associated with the drug with a prominence and readability reasonably comparable with the presentation of information relating to the benefits of the drug. Specifically, the post prominently presents several representations about the benefits of Xeomin in a reel.[4] For example, the reel includes an attention-grabbing presentation of Nate

[4] For the purposes of this letter, the term "reel" refers to a feature of Instagram which allows users to record, edit, and create a post with short-form video content.

Berkus dancing to music as he is getting "ready for a big night out," during which, in his voice over, Berkus states that Xeomin is a "smart tox," and that it "smoothes the look of frown lines" and further implies that it will keep him "looking fresh." The reel also displays the indication and use statement for Xeomin as static, onscreen text at the bottom of the reel throughout the entirety of Nate Berkus's presentation (approximately the first 40 seconds). In contrast, risk information is presented only at the end of the reel, after Nate Berkus says, "see you guys at the next big event" and turns around and walks toward the door at which time the entire screen goes black, which typically signals the close or end of a presentation. In fact, after approximately three seconds of a black screen with no audio, the risk information appears but is presented as onscreen text, using fast-paced[5], scrolling font that is small and difficult to read, which is unlikely to draw the viewer's attention. Additionally, the reel does not present any signal to alert the viewer that important risk information is presented after the close of Nate Berkus's presentation.[6] The overall effect of this presentation undermines the communication of important risk information and thereby misleadingly minimizes the risks associated with the use of Xeomin. OPDP notes that limited risk information is also included in the caption of the post; however, it can only be accessed if the viewer manually scrolls down, past additional benefit claims and other unrelated information. This limited risk information does not mitigate the post's overall misleading minimization of the risk. The presentation in the post is especially problematic from a public health perspective given the serious risks associated with the drug.

False or Misleading Benefit Presentation

Promotional communications misbrand a drug if they are false or misleading with respect to benefits. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts 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 promotional communication.

The reel begins with Nate Berkus inviting viewers to, "Come with me as I get ready for a big night out." Later, the following claims are made in conjunction with scenes of Nate Berkus's preparation routine and eventual departure for an event.

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[5] The first five seconds of scrolling text proceeds through about 220 words which translates to a reading speed of approximately 2,640 words per minute (wpm). From that point on, the following 432 words are scrolled at an estimated reading speed of 5,184 wpm. A recent review and meta-analysis found that the average silent reading rate for adults in English is 238 wpm for uninterrupted non-fiction reading, with most adults falling in a range of 175 to 300 wpm. *See* Brysbaert, Marc. (2019). How many words to we read per minute? A review and meta-analysis of reading rate. 10.31234/osf.io/xynwg. From start to finish, the whole of the scrolling text appears for a total of approximately 28 seconds.

[6] Although the reel includes onscreen text directing viewers to "Swipe left for Important Consumer Safety Information" this action (swiping left) does not direct viewers to any risk information regarding Xeomin.

> Voice over (as Nate Berkus dials a phone in his room): "Keeping my dermatologist on speed dial is my secret weapon for looking fresh. You never know when those lines might decide to make a surprise appearance. That's why she recommended Xeomin . . . that smooths the look of frown lines . . . ."

As the reel plays, the caption includes the statement, "My pro-tips for getting ready for a night out; tuxedo at the ready, fries and Xeomin (incobotulinumtoxinA) @**xeominaesthetic** for smoothing my frown lines" (emphasis original). This presentation misleadingly suggests that Xeomin provides faster or more rapid results than have been demonstrated. In particular, the claims and presentations in the post (reel and caption), suggest that after "a surprise appearance" of frown lines during preparation for a same-day event, treatment with Xeomin is a "secret weapon for looking fresh" and "smoothes the look of frown lines", which can result in achievement of clinical effects in time for a "big night out," when this has not been demonstrated. The efficacy of Xeomin for the temporary improvement in the appearance of moderate to severe glabellar lines was evaluated based on a composite endpoint where treatment success was defined as a 2-grade improvement for both the investigator and patient assessment per the 4-point Facial Wrinkle Scale compared to baseline on Day 30. While efficacy data was also collected at other time points besides the primary endpoint at Day 30, composite endpoint treatment success was not evaluated before day 7. We are not aware of data to support the suggestion that Xeomin can provide successful treatment as rapidly as suggested in the post. If you have data to support this presentation, please submit to FDA for review.

The reel includes a voiceover by Nate Berkus stating that Xeomin is "a double-filtered smart tox that smooths the looks of frown lines with only the ingredients that you need for treatment" (emphasis added). Additionally, the accompanying caption also includes the hashtag, "#SmartTox." These claims misleadingly suggest that due to its manufacturing process and formulation, Xeomin offers benefits over other botulinum toxin products, when this has not been demonstrated. Xeomin is one of multiple botulinum toxin products classified as "acetylcholine release inhibitor and neuromuscular blocking agents" that are FDA-approved for the temporary improvement in the appearance of moderate to severe glabellar lines. We acknowledge that, per the DESCRIPTION section of the PI, the active neurotoxin of Xeomin is "without accessory proteins." However, we are not aware of any head-to-head studies comparing Xeomin to other botulinum toxin products approved to temporarily improve moderate to severe glabellar lines that support claims that Xeomin confers any unique or added benefits as compared to other botulinum toxin products. If you have information or data to support the suggestion that Xeomin's manufacturing process or formulation offers an advantage over other botulinum toxin products in the temporary improvement of moderate to severe glabellar lines, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the post misbrands Xeomin within the meaning of the FD&C Act and make its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). 21 CFR 202.1 (e)(5); (e)(7)(viii).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Merz cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Xeomin that contain representations like those described above, and explaining your plan for the timely discontinuation of such communications, or for ceasing distribution of Xeomin.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us, your reasoning, and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 883 in addition to the BLA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 0724 under BLA 125360. Questions related to the submission of your response letter should be emailed to the OPDP RPM at CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

David Foss, PharmD, MPH, BCPS, RAC
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

{See appended electronic signature page}

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/s/

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