DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Payal Patel, PharmD
Senior Director, Regulatory Affairs
Bausch Health Companies Inc.
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

RE: NDA 209354
DUOBRII™ (halobetasol propionate and tazarotene) lotion, for topical use
MA 178, 221

Dear Dr. Patel:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communications, a direct-to-consumer video and corresponding storyboard (duo-0134-usa-20) (video) and the efficacy webpage[1] of the healthcare professional website (duo-0318-usa-20) (webpage) for DUOBRII™ (halobetasol propionate and tazarotene) lotion, for topical use (Duobrii), submitted by Bausch Health Companies Inc. (Bausch) under cover of Form FDA 2253. The video was originally featured on Lifetime TV's The Balancing Act.[2] The video and webpage make false or misleading claims and/or representations regarding the risks associated with and the efficacy of Duobrii. Thus, the video and webpage misbrand Duobrii within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and make its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(7)(viii). These violations are concerning from a public health perspective because the video fails to include information regarding serious risks associated with Duobrii, a topical product that bears warnings and precautions related to serious systemic risks and serious skin reactions. In addition, the video and webpage create a misleading impression regarding the overall benefit a patient may expect as a result of Duobrii treatment.

Background

Below are the indication and a summary of the most serious and most common risks associated with the use of Duobrii.[3] According to the FDA-approved product labeling (PI):

> DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% is indicated for the topical treatment of plaque psoriasis in adults.

[1] Efficacy webpage located at https://www.duobrii.com/hcp/efficacy (last accessed 03.31.2022).
[2] The video is available on the internet at https://thebalancingact.com/the-latest-in-health-wellness-and-education/ (last accessed 03.31.2022). The video can also be accessed through The Balancing Act's YouTube page, located at https://www.youtube.com/watch?v=NIYpNdPPS94&feature=emb_logo (last accessed 03.31.2022) and Duobrii's consumer webpage, located at https://www.duobrii.com/results (last accessed 03.31.2022).
[3] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

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This product is associated with a number of serious risks. Duobrii is contraindicated in pregnancy. The PI also contains warnings and precautions regarding embryofetal risk, hypothalamic-pituitary-adrenal (HPA) axis suppression and other unwanted systemic glucocorticoid effects, local adverse reactions, photosensitivity and the risk for sunburn, ophthalmic adverse reactions, and concomitant skin infections. The most common adverse reactions reported with Duobrii were contact dermatitis, application site pain, folliculitis, skin atrophy, and excoriation.

Prior Communications

OPDP expressed similar concerns [redacted] (b) (4) for Duobrii [redacted] (b) (4) On February 14, 2020, [redacted] (b) (4) Bausch appears to be promoting Duobrii without presenting the serious risks and efficacy 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.

Video

The video is misleading because it includes efficacy claims for Duobrii but fails to include important risk information associated with the drug. Specifically, the video fails to include material facts regarding the warning and precaution for embryofetal risk. The WARNINGS AND PRECAUTIONS section of the PI states the following (in pertinent part; emphasis added):

> Advise pregnant females of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to DUOBRII Lotion therapy. Initiate DUOBRII Lotion therapy during a menstrual period. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion therapy.

This omission is especially concerning given that the patient, who appears to be of child-bearing age and is seen in the video with two young children, states (emphasis added), "I've been using DUOBRII for 2 years, it works into my routine. I have cleared my plaque psoriasis on my elbows. I didn't have flaky skin, it wasn't sore, it wasn't red. When I have a flare up, I apply it." This claim suggests that a female of reproductive potential can initiate Duobrii or use it whenever she has a psoriasis flare up without regard to the measures needed to mitigate the risk of birth defects associated with Duobrii (i.e., obtain a negative

pregnancy test within two weeks of treatment and use effective birth control to prevent pregnancy during treatment). We acknowledge that some information regarding embryofetal risk is presented in the video; however, this does not mitigate the misleading impression created by the omission of material facts regarding the need for pregnancy testing and birth control from the video.

Moreover, the video fails to include any information regarding the warning and precaution for photosensitivity and the risk for sunburn. This omission is further exacerbated by claims and presentations of a Duobrii-treated patient depicted outside, with exposed shoulders and arms, after discussing the success of her treatment with Duobrii. In earlier scenes, before Duobrii is introduced, the same patient states, “Coworkers, my husband, my kids, even my students would notice my elbow. So, I would wear a lot of three-quarter length even when it was warm outside . . . .” These claims and presentations misleadingly suggest that a patient does not need to take measures to avoid exposure to sunlight after treatment with Duobrii when this is not the case. According to the WARNINGS AND PRECAUTIONS section of the PI (in pertinent part), "Patients must be instructed to use sunscreens and protective clothing when using DUOBRII Lotion.” In addition, the video fails to include any information regarding the warning and precaution for ophthalmic adverse reactions.

By omitting serious risks associated with Duobrii and material facts pertaining to serious risks, the video misleadingly suggests that Duobrii is safer than has been demonstrated.

The video is also misleading because it fails to present information relating to the warnings and precautions for Duobrii with a prominence and readability reasonably comparable with the presentation of information relating to the benefits of Duobrii. For example, important risk information regarding HPA-axis suppression and other unwanted systemic glucocorticoid effects is presented in text-only format in small font relegated to the bottom of the screen. At the same time, benefit claims for Duobrii are prominently presented on the screen in large print while also simultaneously announced verbally by the narrator in the audio portion of the video. The overall effect of disclosing risk information in this manner undermines the communication of important risk information. As a result, the video misleadingly minimizes the risks associated with the use of Duobrii.

False or Misleading Claims about Efficacy

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to efficacy. 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.

Video

In the video, the physician spokesperson makes the following claim regarding the efficacy of Duobrii (emphasis added):

> Adults with plaque psoriasis now have another topical treatment option. Approved by the FDA in 2019, DUOBRII is the first and only topical that combines two active ingredients, both with anti-inflammatory benefits that limit plaque growth.

This claim suggests that Duobrii is the first and only topical combination medication indicated for the treatment of plaque psoriasis that combines two active ingredients, both with anti-inflammatory benefits that limit plaque growth (i.e., FDA-approved for the treatment of plaque psoriasis), when this is not the case. There are other FDA-approved topical combination products (e.g., betamethasone and calcipotriene) marketed prior to Duobrii for the treatment of plaque psoriasis.

The patient spokesperson depicted in the video makes the following claims (emphasis added):

- "I have seen many doctors over the last 11 years for my psoriasis. The creams I was prescribed were thick, and greasy, and they had an odor and they did not work for me."
- "When I first started using DUOBRII, I noticed how light and non-greasy it was. Within days, I started to see results."
- "I've been using DUOBRII for 2 years, it works into my routine. I have cleared my plaque psoriasis on my elbows. I didn't have flaky skin, it wasn't sore, it wasn't red."

Together, these claims are misleading because they suggest that Duobrii is clinically superior to or more effective than other treatments for plaque psoriasis when this has not been demonstrated. In addition, these claims misleadingly imply that Duobrii has been shown to be effective in patients who failed to respond to other plaque psoriasis treatments, when this is not the case. While these claims may be an accurate reflection of the spokesperson's own experience with Duobrii, the personal experience of this patient does not support the suggestion that Duobrii is superior to other plaque psoriasis drugs on the market. According to the CLINICAL STUDIES section of the PI, the pivotal trials of Duobrii evaluated Duobrii versus vehicle lotion, not versus any other treatments for plaque psoriasis. Moreover, the pivotal trials of Duobrii excluded patients with psoriasis that failed to respond to prescription medication, even partially or temporarily, as determined by the investigator.[4] Therefore, the available data do not support the suggestions that Duobrii is superior to or more effective than other plaque psoriasis treatments on the market and that Duobrii has been shown to be effective in patients who have failed other plaque psoriasis treatments. FDA is not aware of evidence to support these claims. If you have data to support these claims, please submit them to FDA for review. We acknowledge that the video includes the SUPER, "People with psoriasis may respond to treatments differently and at different times. Individual results may vary." However, this does not mitigate the misleading impression.

[4] Data on File. Trials 301 and 302 Clinical Study Reports.

Webpage

The webpage makes claims and presentations such as the following regarding the efficacy of Duobrii (bolded and italicized emphasis original, underlined emphasis added):

- "**Demonstrated synergy: superior efficacy vs the aggregated results of two monotherapies[5]**"
- A graph entitled, "Treatment success[6] at 8 weeks with the effect of the vehicle removed.[7]"
    - A bar graph that depicts "treatment success" as 42.8% for Duobrii Lotion and 32.5% for the monotherapies aggregated, after the vehicle results are removed.
- "**More patients experienced treatment success[8] with DUOBRII Lotion than the aggregated success rates of both monotherapies[9]**"
- "DUOBRII Lotion exceeded the clinical definition of synergy by 31.7% at 8 weeks[10,11]"

The webpage creates a misleading impression regarding the efficacy and mechanism of action of Duobrii because it draws conclusions based on data that are inadequate to support such conclusions. The claims of "demonstrated synergy" and "superior efficacy" versus the aggregated results of two monotherapies on the webpage are based on data derived from post hoc analyses of a single phase 2 trial, of limited sample size, which compared Duobrii separately to its individual components and vehicle. We acknowledge the statement, "Post hoc analysis of a phase 2 clinical trial" is included on the webpage. However, this does not mitigate the misleading impression created by these claims and presentations because the phase 2 trial was not designed to support conclusions comparing the efficacy of Duobrii to its aggregated components, minus the vehicle effect. Because this analysis was conducted post hoc, there was no prespecified statistical procedure controlling for type 1 error rate (false positive rate) in this phase 2 trial, so it is not possible to ascertain whether the findings were attributable to treatment with Duobrii and its components, or merely due to chance. As a result, these findings are exploratory (hypothesis-generating). Therefore, claims and presentations that draw conclusions (e.g., "demonstrated synergy" and/or "superior efficacy") are misleading.

Furthermore, this presentation of data regarding the phase 2 trial is misleading because it overstates the efficacy of the drug by inaccurately describing treatment success at 8 weeks. Specifically, the claims and presentation imply that the difference in efficacy between Duobrii and the aggregate of tazarotene and halobetasol (its individual components) was 10.3%,

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[5] Kircik LH, Papp KA, Stein Gold L, et. al. 2019. Assessing the Synergistic Effect of a Fixed Combination Halobetasol Propionate 0.01% and Tazarotene 0.045% Lotion in Moderate-to-Severe Plaque Psoriasis1. *J Drugs Dermatol* 2019;18(3):279-284.
[6] Treatment success was defined as at least a 2-grade improvement from baseline in Investigator Global Assessment (IGA) score and an IGA score equating to "clear" or "almost clear" at Week 8.
[7] See footnote 5.
[8] See footnote 6.
[9] See footnote 5.
[10] See footnote 5.
[11] Sugarman JL, Gold LS, Lebwohl MG, et al. A phase 2, multicenter, double-blind, randomized, vehicle controlled clinical study to assess the safety and efficacy of a halobetasol/tazarotene fixed combination in the treatment of plaque psoriasis. J Drugs Dermatol. 2017;16(3):611-618.

when the absolute difference between Duobrii and the aggregate of its individual components was only 0.6% in the actual topical lotion dosage form used in the phase 2 trial (52.5% vs 51.9%). In the trial, Duobrii and its components were administered topically in the same vehicle lotion, which provided a 9.7% response rate. However, the webpage presents results that were analyzed post hoc after the 9.7% vehicle lotion response rate was removed from Duobrii and each of its individual components.[12] This webpage, therefore, presents a much larger difference in efficacy between treatment arms than was actually demonstrated. As a result, this presentation is misleading.

Conclusion and Requested Action

For the reasons discussed above, the video and webpage misbrand Duobrii within the meaning of the FD&C Act and make its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(7)(viii).

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

If you believe that your product is 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 178 and MA 221 in addition to the NDA 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.

[12] Duobrii and its individual components are unavailable for commercial use in this manner.

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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 5057 under NDA 209354. 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}

Laurie Buonaccorsi, Pharm.D.
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

{See appended electronic signature page}

Matthew J. Falter, Pharm.D.
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/s/

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