FDA Targets Prescription Drug Promotions Again:

An Update on Compliant Promotional Material and Enforcement Implications

Presented by Rebecca Zadaka, J.D., M.A. Bioethics

Thursday, September 28, 2023

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Presenter Introduction

Rebecca Zadaka specializes advising FDA-regulated clients in regulatory matters, particularly advertising and promotion. Before practicing at Gardner Law, Rebecca worked as a litigation attorney in business litigation.

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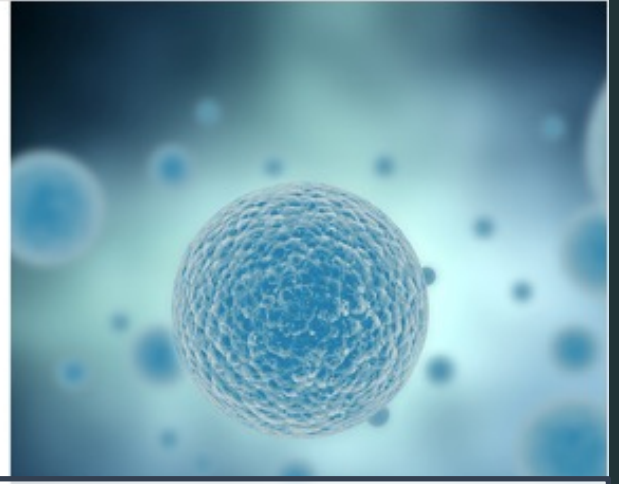
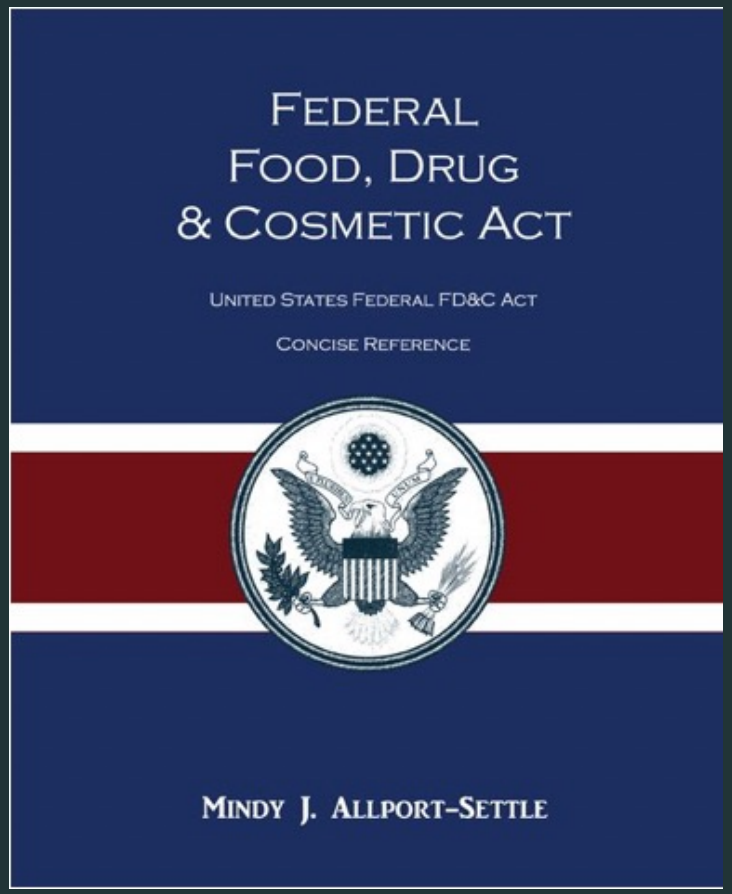
Agenda

- What is “advertising and promotion?”
- U.S. regulatory oversight of advertising and promotion
- Risks of non-compliant promotion
- A deeper look into this summer’s Untitled and Warning Letters
- Implications
- Q&A



What is advertising and promotion in the device and pharma world?

First Question: What is "labeling?"



"Label"

"a display of written, printed, or graphic matter upon the immediate container of any article"

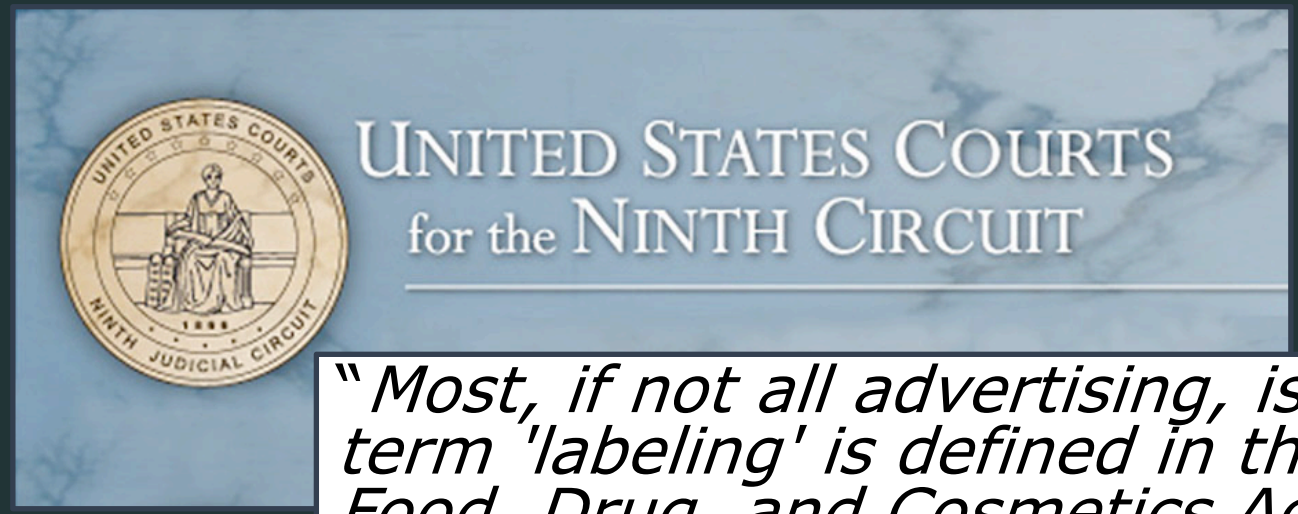
FFDCA § 201(k)

"Labeling"

"all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article"

FFDCA § 201(m)

Next Question: When does advertising become "labeling?"



"*Most, if not all advertising, is labeling. The term 'labeling' is defined in the [Federal Food, Drug, and Cosmetics Act] as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising*."

United States v. Research Laboratories, 126 F.2d 42 (9th Cir. 1942)

Forms of Promotional Labeling

- Sell sheets (“one-pager”)
- Product videos
- Patient testimonials
- Convention booths
- Websites
- Product brochures
- Search engine promotions
- Product mailings
- TV and print advertisements
- Social media
- Certain interactions (including oral or written interactions) with patients or physicians at product events or industry conventions

… Any communication created, sponsored, or distributed by a company discussing its products may be considered promotional labeling.

U.S. Regulatory Oversight of Device/Drug Advertising and Promotion

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Regulatory Oversight

FDA

Primary regulatory agency overseeing device/drug advertising

FTC

Regulatory agency overseeing product advertisement and trade generally

Fundamental FDA Advertising Prohibition

21 U.S. Code § 352 – Misbranded drugs and devices

A drug or device shall be deemed to be misbranded --

(a) False or Misleading Label

1) If its labeling is false or misleading in any particular.

Fundamental Drug-Specific FDA Advertising Prohibition

21 C.F.R. Part 202(e)(1)– Prescription Drug Advertising: *When Required*

All advertisements for any prescription drug . . . shall present a true statement of information in brief summary relating to side effects, contraindications . . . and effectiveness.

Fundamental Drug-Specific FDA Advertising Prohibition

21 C.F.R. Part 202(e)(3)– Prescription Drug Advertising: *Scope of information to be included; applicability to the entire advertisement.*

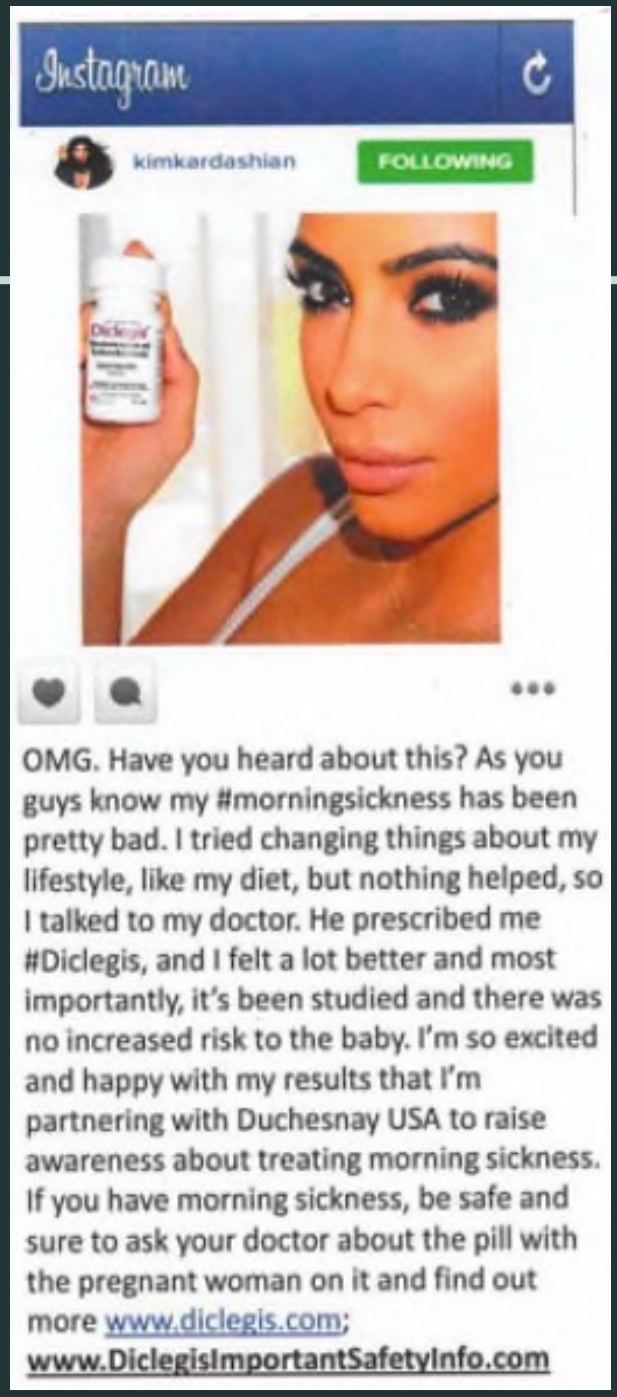
(i) The requirement of a true statement of information relating to side effects, contraindications, and effectiveness applies to the entire advertisement. Untrue or misleading information in any part of the advertisement will not be corrected by the inclusion in another distinct part of the advertisement of a brief statement containing true information relating to side effects, contraindications, and effectiveness of the drug. . . .

Examples of False and Misleading Labeling

- Incorrect (or “half-true”) statements regarding the device/drug or its outcomes
- Unsubstantiated claims regarding therapeutic outcomes or superiority
- Ambiguous claims intended to create an “implied claim”
- Subjective statements that cannot be substantiated
- Withholding of material facts (e.g., risks of use of the device, contradictory clinical evidence or opinion)
- Misleading or extraordinary physician and patient testimonials

An Example


Kim Kardashian West
@KimKardashian
Follow
OMG. Have you heard about this? As you guys know my #morningsickness has been pretty bad. I tried…
instagram.com/p/5Vr42NOS0B/
9:14 PM - 19 Jul 2015
568
2,370


Instagram
kimkardashian
FOLLOWING
OMG. Have you heard about this? As you guys know my #morningsickness has been pretty bad. I tried changing things about my lifestyle, like my diet, but nothing helped, so I talked to my doctor. He prescribed me #Diclegis, and I felt a lot better and most importantly, it's been studied and there was no increased risk to the baby. I'm so excited and happy with my results that I'm partnering with Duchesnay USA to raise awareness about treating morning sickness. If you have morning sickness, be safe and sure to ask your doctor about the pill with the pregnant woman on it and find out more www.diclegis.com;
www.DiclegisImportantSafetyInfo.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

TRANSMITTED BY FACSIMILE

Eric Gervais, Executive Vice President
Duchesnay, Inc.
919 Conestoga Road
Building One, Suite 203
Rosemont, PA 19010

WARNING LETTER

Dear Mr. Gervais:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the Kim Kardashian Social Media Post (social media post) (2015-0069-01) [1] for DICLEGIS (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets, for oral use (DICLEGIS) submitted by Duchesnay, Inc. (Duchesnay) under cover of Form FDA 2253. The social media post was also submitted as a complaint to the OPDP Bad Ad Program. The social media post is false or misleading in that it presents efficacy claims for DICLEGIS, but fails to communicate any risk information associated with its use and it omits material facts. Thus, the social media post misbrands DICLEGIS 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). *See* 21 CFR 202.1(e)(5). These violations are concerning from a public health perspective because they suggest that DICLEGIS is safer than has been demonstrated.

Consequences for Misbranding Drugs and Devices

- Government investigation (e.g., for cause inspection by FDA or referral to the Office of Inspector General and/or Department of Justice)
- Warning Letters and Untitled Letters
- Recalls and suspension of Certificates to Foreign Government ("CFG")
- Seizure, detention, reconditioning, forfeiture, and/or destruction of product
- Publicity
- Judicial actions (disgorgement of profits, restitution, liquidated damages)
- Civil and criminal consequences under the FDCA
  - Fines and/or jail time for company and/or employees
- Debarment
- Withdrawal of product approvals
- Suspension of new product applications (or, practically speaking, tainting of new product applications)
- Other potential consequences
  Exclusion (under Social Security Act)
  Shareholder lawsuits
  State consumer protection liability
  Product liability
  Federal Trade Commission, Lanham Act, and state law exposure
  Internal issues, such as CAPA

Untitled Letters and Warning Letters

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Untitled Letter

- An untitled letter is a pre-warning letter sent to a company
- It is usually sent for issues that do not meet the regulatory threshold for a warning letter
- They do not require corrective dissemination but do ask that any violations be ceased
- Lets the company know that FDA is aware of the company's violation(s)

Warning Letter

- A warning letter requires a corrective action, and if not, FDA enforcement may result
- A warning letter will come when the issues that need to be corrected are of greater regulatory significance
- FDA may also send a warning letter if there is a history FDA has with the company on the issue

OPDP’s lull in sending untitled letters

- Up until this summer, OPDP had not sent an untitled letter in a little over a year
- 2020 saw a decline in untitled letters, but none for as long or quiet as summer 2022 to 2023
- Many recent letters have pertained to whether the promotional materials are consistent with the approved labeling

2023’s Untitled and Warning Letters

And now for a deeper analysis of 2023’s Untitled and Warning Letters

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Untitled Letter 1
Xeris Pharmaceuticals re Recorlev

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Xeris Pharmaceuticals, Inc.
Attention: Michele Yelmene
Vice President, Global Regulatory Affairs & Operations
900 Northbrook Drive, Suite 200
Trevose, PA 19053

RE: NDA 214133
RECORLEV (levoketoconazole) tablets, oral
MA 14

Dear Michele Yelmene:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communications, the "What is Recorlev®?" and "Taking Recorlev®" webpages[1] of the consumer website (US-REC-21-00033 [v1.0]) (webpages) for RECORLEV (levoketoconazole) tablets, oral (Recorlev) submitted by Xeris Pharmaceuticals, Inc. (Xeris) under cover of Form FDA 2253. The webpages make false or misleading claims and representations about the safety and efficacy of Recorlev. Thus, the webpages misbrand Recorlev within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), making its distribution violative. 21 U.S.C. 352(a), (n); 321(n), 331(a). See 21 CFR 202.1(e)(3)(i); (e)(5). These violations are especially concerning from a public health perspective because the promotional communications create a misleading impression regarding the safety and effectiveness of Recorlev, a drug with a number of serious and potentially life-threatening risks, including boxed warnings regarding the risks of hepatotoxicity and QT prolongation.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Recorlev.[2] According to the INDICATIONS AND USAGE section of the FDA-approved prescribing information (PI):

> RECORLEV is indicated for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative.
>
> Limitations of Use
> RECORLEV is not approved for the treatment of fungal infections. The safety and effectiveness of RECORLEV for the treatment of fungal infections have not been established.

The PI for Recorlev contains boxed warnings regarding the risks of hepatotoxicity and QT prolongation. Recorlev is contraindicated in patients with cirrhosis, acute liver disease or poorly controlled chronic liver disease, baseline AST or ALT greater than 3 times the upper limit of normal, recurrent symptomatic cholelithiasis, a prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy that required discontinuation of treatment, or extensive metastatic liver disease; in patients taking drugs that cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes; in patients with a prolonged QTcF interval of greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history); in patients with known hypersensitivity to levoketoconazole, ketoconazole or any excipient in RECORLEV; and in patients taking certain drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P-gP. In addition, the PI for Recorlev includes warnings and precautions regarding hypercortisolism, hypersensitivity reactions, and risks related to decreased testosterone. The most common adverse reactions (incidence > 20%) reported with Recorlev were nausea/vomiting, hypokalemia, hemorrhage/contusion, systemic hypertension, headache, hepatic injury, abnormal uterine bleeding, erythema, fatigue, abdominal pain/dyspepsia, arthritis, upper respiratory infection, myalgia, arrhythmia, back pain, insomnia/sleep disturbances, and peripheral edema.

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.

The "What is Recorlev®?" webpage includes the following presentation regarding the SONICS study (emphasis original):

- "**The SONICS clinical study supported the efficacy and safety results from LOGICS**"
  - "**31%** of patients had normal cortisol levels after taking Recorlev for 6 months without changing their dose"
  - "**67%** of patients who moved on to the second part of the study had normal cortisol levels by the end of the study"

The claim, "**67%** of patients who moved on to the second part of the study had normal cortisol levels by the end of the study" (emphasis original), misleadingly overstates the efficacy of Recorlev. According to the CLINICAL STUDIES section of the PI, the SONICS study (Study 2) consisted of three phases (dose titration, maintenance, and extended evaluation). Out of the 94 patients who enrolled in the study and entered the dose titration phase, 77 patients "moved on to the second part of the study" (i.e., maintenance phase). At the end of the maintenance phase, only 29 of those 77 (38%) patients had normal cortisol levels. By the end of the extended evaluation phase, the number of patients with normal cortisol levels decreased to 16 of those 77 (21%) patients. We acknowledge that according to the PI, 67% of patients in the SONICS study had normal cortisol levels at the end of the titration phase; however, the titration phase was not the "end of the study." In addition, regardless of whether the end of the maintenance phase or extended evaluation phase is considered the "end of the study," both phases failed to attain the results claimed on the webpage, with 38% and 21% of patients reaching normal cortisol levels, respectively, rather than 67%. Therefore, suggesting that 67% of patients who "moved on to the second part of the study" had normal cortisol levels by the end of the study significantly overstates the efficacy of the product.

Furthermore, the presentation omits material information necessary to interpret any study results from the SONICS study (Study 2). Specifically, the CLINICAL STUDIES section of the PI states, "[b]ecause 51% of patients discontinued treatment prematurely due to adverse reaction, lack of efficacy, or other reasons, these results should be interpreted with caution." The omission of this material information from the webpage undermines the ability of the reader to understand and evaluate the study results presented and thereby creates a misleading impression about the drug's efficacy.

The "What is Recorlev®?" webpage also includes the following claim regarding the LOGICS study (emphasis original):

- "**Recorlev** - More patients (52%) who were on a stable and steady dose of Recorlev had normal cortisol levels"

This claim creates a misleading impression regarding the efficacy of Recorlev because it implies that the results represent the general experience of patients with the drug. On the contrary, the results presented are based on a small, select subset of patients enrolled in the study who had already demonstrated that they were able to tolerate and respond to the drug.

According to the CLINICAL STUDIES section of the PI, the LOGICS study (Study 1) consisted of two phases, a dose titration and maintenance phase followed by a randomized withdrawal phase. Seventy-nine patients entered the dose titration and maintenance phase. Patients who achieved a stable therapeutic dose for at least 4 weeks and achieved a normal mean urinary free cortisol (i.e., "normal cortisol levels") at the end of the dose titration and maintenance phase were eligible for the withdrawal phase. Only 39 patients with "normal cortisol levels" entered the withdrawal phase (37 from the dose titration and maintenance phase of the LOGICS study and 2 directly from a separate study as allowed by the LOGICS study design). Over half of the patients who entered the titration and maintenance phase of the LOGICS study discontinued for various reasons, including experiencing adverse reactions and lack of efficacy. Of the 39 patients that continued to the withdrawal phase of the study, 21 were randomized to Recorlev, and 18 to placebo. It is only out of those 21 patients in the Recorlev group (from the 79 that underwent dose titration) that 52% (11/21) achieved "normal cortisol levels" at the end of the withdrawal phase. Thus, it is misleading to suggest that the results from this enriched patient population represent the general experience expected in patients who take Recorlev.

False or Misleading Risk Presentation

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.

The "Taking Recorlev®" webpage includes the following presentation under the header "**Monitoring and side effects**" (emphasis original):

- "**Monitoring**"

  "**As with other medicines for Cushing's, monitoring by your doctor is important so they know how you're doing**"

  . . .

  "Heart and liver tests before and during treatment with Recorlev will help your doctor avoid side effects"

- "**Possible side effects**"

  "**Side effects can occur with Recorlev, including some that are serious**"

This presentation minimizes the serious and significant risks associated with the use of Recorlev by acknowledging that "[s]ide effects can occur with Recorlev, including some that are serious," without discussing information regarding Recorlev's boxed warnings or specific side effects associated with the drug, including those that are potentially fatal. Additionally, this presentation suggests that heart and liver tests alone will enable patients to "avoid" side effects altogether. As noted above, the PI for Recorlev includes boxed warnings for hepatotoxicity and QT prolongation. The risk of hepatotoxicity has been associated with use

of oral ketoconazole[3] and has led to fatal outcomes or the need for liver transplantation. Similarly, the risk of QT prolongation associated with Recorlev has resulted in life-threatening ventricular dysrhythmias. The webpage's presentation is especially concerning given that a number of patients taking Recorlev in clinical studies experienced these potentially life-threatening side effects. For example, the WARNINGS AND PRECAUTIONS section of the PI states that 13% of patients using Recorlev experienced drug-induced liver injury, and 14.7% of patients experienced a change-from-baseline QTcF >60 msec. The PI also notes that Recorlev is associated with multiple other serious and potentially life-threatening risks unrelated to heart or liver problems, as well as numerous common adverse reactions, many of which occurred in more than 20% of patients treated with the drug.

We acknowledge that risk information for Recorlev is presented separately in the "INDICATION AND IMPORTANT SAFETY INFORMATION" section of the webpage. However, this does not mitigate the misleading impression created by the "Monitoring and side effects" presentation because the boxed warnings are relegated to the middle of this consolidated risk section, after the contraindications and indication and use statement, and without any significant signal to alert the viewer to them. The overall effect of this webpage's presentation of risk information undermines the communication of the significant and potentially fatal risks associated with Recorlev and thereby misleadingly minimizes the risks associated with the use of Recorlev.

Conclusion and Requested Action

For the reasons discussed above, the webpages misbrand Recorlev 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).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Xeris 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 Recorlev that contain representations like those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Recorlev.

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.

Untitled Letter 2
Exeltis USA Inc. re Slynd

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Jenny McNeil, PharmD, Regulatory Affairs Associate
Exeltis USA Inc.
180 Park Avenue, Suite 101
Florham Park, NJ 07932

RE: NDA 211367
SLYND (drospirenone) tablets, for oral use
MA 40

Dear Dr. McNeil:

As part of its monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a promotional communication, a social media sponsored post (EXS-22-64 R00) (post), for SLYND (drospirenone) tablets, for oral use (Slynd).[1] The post makes false or misleading claims and representations about the risks and efficacy of Slynd. Thus, the post misbrands Slynd 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). *See* 21 CFR 202.1(e)(5). In addition, this material was not submitted at the time of initial dissemination or publication as required by 21 CFR 314.81(b)(3)(i). These violations are concerning from a public health perspective because the promotional communication fails to include any risk information, which creates a misleading impression about the expected benefits and safety of Slynd.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Slynd.[2] According to the INDICATIONS AND USAGE section of the FDA-approved prescribing information (PI)[3]:

> SLYND is a progestin indicated for use by females of reproductive potential to prevent pregnancy.

Slynd is contraindicated in females with renal impairment; adrenal insufficiency; presence or history of cervical cancer or progestin sensitive cancers; liver tumors, benign or malignant, or hepatic impairment; and undiagnosed abnormal uterine bleeding. The PI for Slynd includes warnings and precautions regarding hyperkalemia, thromboembolic disorders, bone loss, cervical cancer, liver disease, ectopic pregnancy, risk of hyperglycemia in patients with diabetes, bleeding irregularities and amenorrhea, and depression. The most common adverse reactions reported with Slynd were acne, metrorrhagia, headache, breast pain, weight increase, dysmenorrhea, nausea, vaginal hemorrhage, libido decreased, breast tenderness, and menstruation irregular[ity].

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.

The post, titled "Slynd® (drospirenone)," is misleading because it presents claims and representations about the benefits of Slynd but fails to communicate **any** risk information. By omitting the risks associated with Slynd, the post fails to provide material information about the consequences that may result from the use of Slynd and creates a misleading impression about the drug's safety.

False or Misleading Claims about Efficacy

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.

The post includes the following claim (emphasis original):

- "**Offer your patients estrogen-free birth control with periods on a schedule.**"

This claim is misleading because it overstates the efficacy of Slynd by claiming patients will have a "period," or bleeding, that is predictable and "on a schedule" when this has not been demonstrated. We note that, according to the CLINICAL STUDIES section of the Slynd PI, in Study CF111/303, 81.2% of patients had scheduled[4] bleeding in Cycle 1. However, this **decreased** to 26.4% after 13 cycles of treatment with Slynd. Similarly, in Study CF111/304, scheduled bleeding also **decreased** over time from 98.0% in Cycle 1 to 28.4% in Cycle 13. Thus, the majority of patients did **not** experience "periods on a schedule" over the duration of treatment with Slynd. Rather, "periods on a schedule" decreased. In addition, Slynd is associated with bleeding irregularities and amenorrhea. According to the WARNINGS AND PRECAUTIONS section of the Slynd PI, "Females using SLYND may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first three months of use." In fact, a large proportion of patients (40.3% and 52.2% in Studies CF111/303 and CF111/304, respectively) still reported unscheduled[5] bleeding after 13 cycles of treatment. Thus, "periods" and other occurrences of bleeding were **not** "on a schedule." Therefore, due to the majority of patients not experiencing scheduled bleeding (as would be expected during a menstrual cycle) during treatment with Slynd and the large proportion of patients still experiencing breakthrough bleeding, claims regarding Slynd patients experiencing predictable or "scheduled periods" are not supported by the data. If you have information or data to support periods occurring on a schedule, please submit to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the post misbrands Slynd 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)(5). Furthermore, Exeltis did not comply with 21 CFR 314.81(b)(3)(i).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Exeltis 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 other promotional communications (with the 2253 submission date) for Slynd that contain representations such as those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Slynd.

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.

Warning Letter
AstraZeneca Pharmaceuticals re Breztri Aerosphere

RE: NDA 212122
BREZTRI AEROSPHERE™ (budesonide, glycopyrrolate, and formoterol fumarate) inhalation aerosol, for oral inhalation use MA 385

WARNING LETTER

Dear Pascal Soriot:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a promotional communication, a professional sales aid (US-68433), for BREZTRI AEROSPHERE™ (budesonide, glycopyrrolate, and formoterol fumarate) inhalation aerosol, for oral inhalation use (Breztri) submitted by AstraZeneca under cover of Form FDA 2253. The sales aid makes false or misleading claims and/or representations about the efficacy of Breztri. Thus, the sales aid misbrands Breztri 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); 331(a). Cf. 21 CFR 202.1(e)(5). These violations are concerning from a public health perspective because the promotional communication creates a misleading impression regarding the overall benefits a patient may expect as a result of Breztri treatment.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Breztri.[1] According to the FDA-approved Prescribing Information (PI):

BREZTRI AEROSPHERE is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Limitations of Use:

BREZTRI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Breztri is contraindicated in patients who have demonstrated hypersensitivity to budesonide, glycopyrrolate, formoterol fumarate, or any of the excipients. The PI for Breztri includes the following Warnings and Precautions: serious asthma-related events—hospitalizations, intubations, and death; deterioration of disease and acute episodes; avoid excessive use of Breztri and avoid use with other long-acting beta2-agonists; oropharyngeal candidiasis; pneumonia; immunosuppression and risk of infections; transferring patients from systemic corticosteroid therapy; hypercorticism and adrenal suppression; drug interactions with strong cytochrome P450 3A4 inhibitors; paradoxical bronchospasm; hypersensitivity reactions including anaphylaxis; cardiovascular effects; reduction in bone mineral density; glaucoma and cataracts, worsening of narrow-angle glaucoma; worsening of urinary retention; coexisting conditions; and hypokalemia and hyperglycemia. The most common adverse reactions reported with use of Breztri are upper respiratory tract infection, pneumonia, back pain, oral candidiasis, influenza, muscle spasm, urinary tract infection, cough, sinusitis, and diarrhea.

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.

The sales aid includes the prominent headline claim (emphasis original), "**DIFFERENCE OBSERVED IN TIME TO ALL-CAUSE MORTALITY (OVER 52 WEEKS)**," in conjunction with a graph titled, "**SECONDARY ENDPOINT STUDY 1: Time to all-cause mortality in the ITT**

population," and the following claims (emphasis original):

- "**An observed relative difference with BREZTRI vs LAMA/LABA was shown in data published in 2020/2021, including in the *New England Journal of Medicine***"
- "**49% Observed relative difference with BREZTRI vs LAMA/LABA**"

These claims and presentation, in the context of a promotional communication describing the safety and efficacy of Breztri, are misleading because they suggest that Breztri treatment has been shown to have a positive impact on all-cause mortality (ACM) and reduce the risk of death in COPD patients. These suggestions are not supported by the cited references[2,3] that analyzed data from the Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) trial. The ETHOS trial was designed with ACM as one of multiple secondary endpoints, and due to the failure of the study to show statistically significant results on endpoints higher in the analysis hierarchy, the trial does not allow for any conclusions to be drawn from the ACM data. In addition, as the ETHOS study design required removing patients from inhaled corticosteroids (ICS) prior to entering a treatment arm, abrupt withdrawal of ICS may have been a confounding factor when analyzing any positive effect on ACM. Due to the statistical testing hierarchy failure and to the fact that abrupt withdrawal of ICS may have been a confounding factor, no conclusions about the effect of Breztri on ACM can be drawn from the ETHOS trial. We note the statement below the graph, "These results are observational in nature, and any comparisons between treatment arms should be interpreted with caution." However, this does not mitigate the misleading impression. To date, no drug has been shown to improve ACM in COPD.[4] The results of the ETHOS trial do not exclude the possibility that the benefits in ACM claimed above may be attributable to chance or to the withdrawal of ICS and not due to Breztri. These claims and presentation are concerning from a public health perspective because they overstate the efficacy of the drug and misleadingly suggest that Breztri will have a positive impact on ACM and reduce the risk of death in COPD patients.

- "In a 52-week study where patients had a history of exacerbations within the last year, **BREZTRI was the ONLY triple therapy vs ICS/LABA to show a significant reduction in severe exacerbations**"
- "**20% EXACERBATION REDUCTION VS ICS/LABA**[;] rate ratio: 0.80[;] *P=0.02*"

The presentation of these claims with the associated p-value creates a misleading impression regarding the benefit of the drug by suggesting that Breztri will have a statistically significant reduction in severe exacerbations. This suggestion is not supported by the ETHOS trial data analyzed in the cited reference[5] because the reduction in severe exacerbations was not statistically significant for patients treated with Breztri relative to comparator groups. A pvalue is generally understood to indicate statistical significance if it is less than 0.05. Therefore, the inclusion of a p-value of 0.02 in conjunction with the above presentation creates the impression that the reduction in severe exacerbations was statistically significant. However, for the Breztri to inhaled corticosteroid/long-acting beta agonist (ICS/LABA) comparison (i.e., "20% REDUCTION VS ICS/LABA"), the result was not statistically significant due to the p-value being greater than the significance threshold (critical value) established in the testing strategy. In the ETHOS trial[6] testing strategy the raw p-value of each hypothesis test was compared to the corresponding critical value to determine whether the test was statistically significant. As the p-value for the Breztri to ICS/LABA comparison (p=0.02) was greater than the critical value (0.008) for that hypothesis test, the result, per the threshold set by the testing strategy, is not statistically significant. Therefore, the presentation of these claims (i.e., with a p-value of 0.02) creates

Conclusion and Requested Action

For the reasons discussed above, the detail aid misbrands Breztri within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a); 331(a). Cf. 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that AstraZeneca 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 other promotional communications (with the 2253 submission date) for Breztri that contain representations such as those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Breztri.

Failure to adequately address this matter may lead to regulatory action. 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.

Additionally, we request that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective communication(s) about the concern(s) discussed in this letter. The corrective communication(s) should be disseminated to the audience(s) that received the promotional communication(s) identified in the opening paragraph of this letter. OPDP recommends that corrective communication(s) include a description of the promotional communication(s) identified in this letter, which misbrand Breztri; include a summary of the concern(s) described in this letter; and provide information to correct each of these concern(s). Corrective communication(s) should be free of promotional claims and presentations. To the extent possible, corrective communication(s) should be distributed using the same media, and generally for the same duration of time and with the same frequency as the promotional communication(s) identified in the opening paragraph 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.

Summary of the 2023 letters

- To summarize, FDA’s letter show that FDA is not ignoring bad ads despite its hiatus
- In fact, FDA is scouring the data, as shown from these letters; fine data points are identified

Implications

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What do these 2023 letters mean for device/drug companies?

- These letters serve as a reminder that FDA is seeing ads and is reviewing them critically
- Drug and device companies have a chance to look critically at their ads
  - Are they compliant?
  - Not only do they have all required and material information, but are statements presenting materially truthfully?

Questions?

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