Regulatory Education for Industry (REdI):

PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES

Bethesda Marriott | Pooks Hill, MD | November 3-4, 2015

Drug Labeling and Its Impact on Promotion

Office of Prescription Drug Promotion (OPDP)
Food and Drug Administration

Office of Promotion and Advertising Review
Merck & Co., Inc.

Drug Labeling and Its Impact on Promotion

Moderator

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CDR Aline Moukhtara
Regulatory Review Officer

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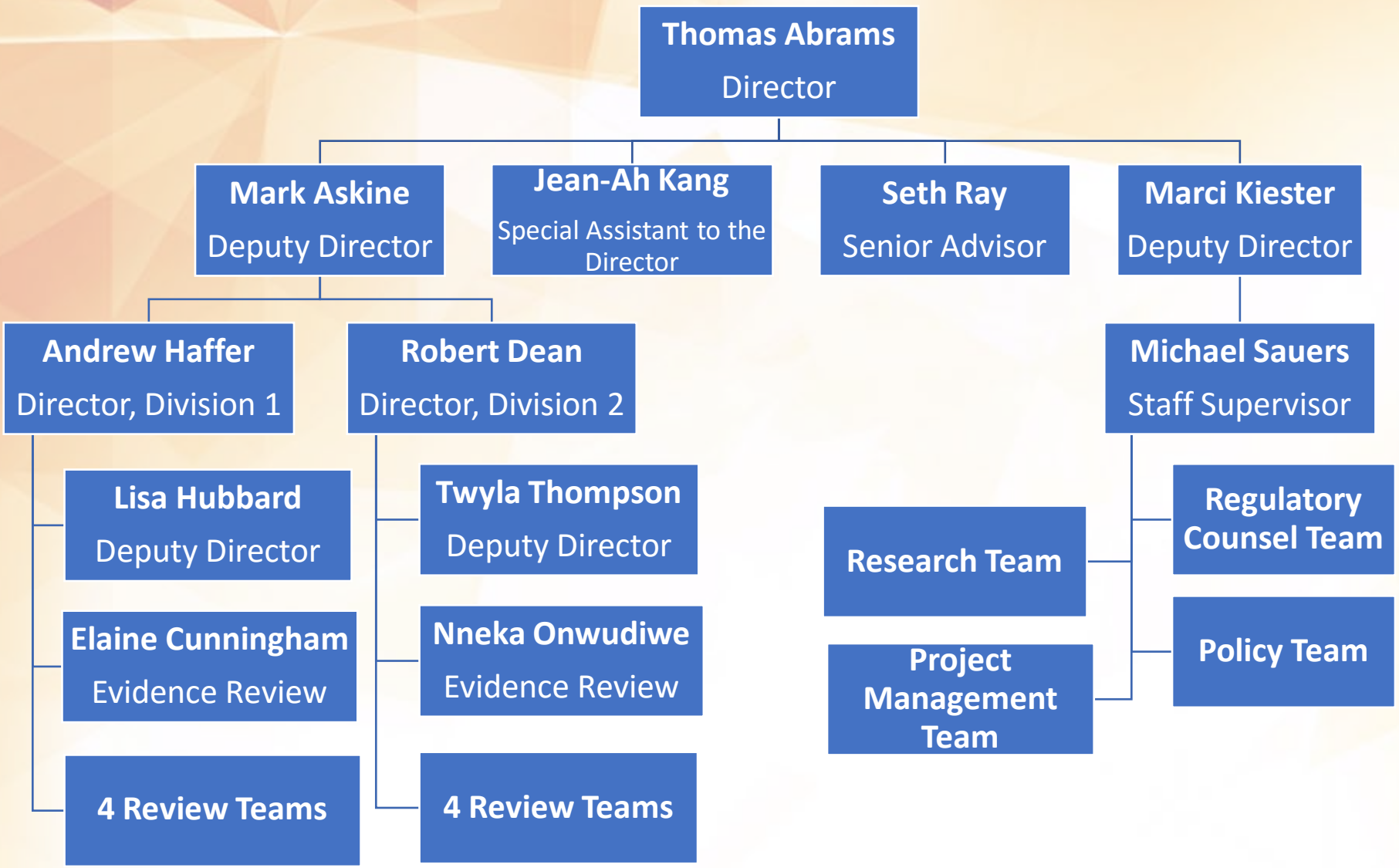
Senior Advisor for Evidence Review

Office of Prescription Drug Promotion (OPDP)
Food and Drug Administration

OPDP's Mission and Objectives

- **Mission**
  - Protect the public health by ensuring that prescription drug information is truthful, balanced, and accurately communicated
- **Objectives**
  - Ensure that prescription drug promotion is not false or misleading
  - Ensure that balanced picture of drug is conveyed
  - Aid in the communication of more useful information about drugs and diseases to the American public

OPDP Organization Chart



OPDP's Role

- Compliance with Federal Food Drug & Cosmetic Act and Code of Federal Regulations
- Advice to industry and within FDA
- Surveillance
- Guidances and policy development
- Research
- Enforcement

Bad Ad Program

- FDA-sponsored outreach program designed to increase awareness of healthcare professionals (HCPs) about the role they can play in helping FDA ensure that prescription drug promotion is truthful and not misleading
- When HCPs have concerns about prescription drug promotion, they can report it to FDA:
  - Call
    - **855-RX-BadAd**
  - E-mail
    - **BadAd@fda.gov**
- Continuing Education Program for HCPs
  - Physicians, pharmacists, nurses, physician assistants, nurse practitioners

Regulations

Prescription Drug Advertising
(21 CFR 202.1)

- Not be false or misleading
- Consistent with FDA-approved product labeling
- Supported by an appropriate level of evidence
- Present a fair balance between efficacy and risk information
- Reveal facts material with respect to consequences that may result from the use of the drug as recommended or suggested

Regulations

Requirements on content and format of labeling for human prescription drug and biological products

(21 CFR 201.56(a)(2))

". . . . The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. . . ."

OPDP's Role in Product Labeling

- OPDP reviews draft drug labeling for promotional implications, in collaboration and consultation with various entities within the FDA.
- Labeling is a critical component for prescription drug promotion.

Product Labeling and Prescription Drug Promotion

- The FDA-approved product labeling is an integral part for reviewing proposed promotional materials when Sponsors request advisory comments, and for evaluating promotional claims in the public domain.

TussiCaps® Product Labeling and Enforcement Example

- **Warning Letter** (July 27, 2015, professional sales aid)
- **Indication**
  - For relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older
- **Contraindications**
  - Patients with a known allergy or sensitivity to hydrocodone or chlorpheniramine
  - Children less than 6 years of age due to the risk of fatal respiratory depression

TussiCaps® Product Labeling and Enforcement Example

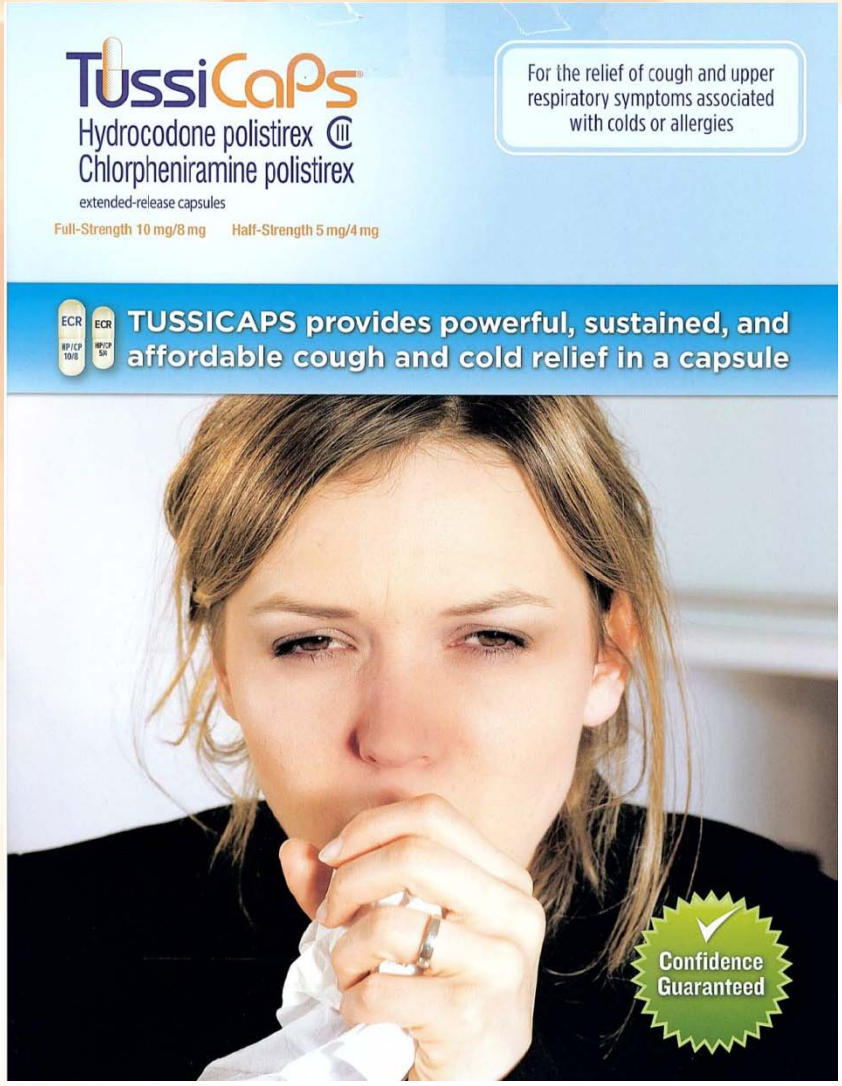
- **Warnings**
  - Respiratory depression, head injury and increased intracranial pressure, acute abdominal conditions, obstructive bowel disease, and pediatric use

- **Precautions**
  - Patients with narrow-angle glaucoma, asthma, or prostatic hypertrophy, elderly or debilitated patients, and patients with severely impaired hepatic or renal function, hypothyroidism, Addison's disease, or urethral stricture

TussiCaps® Product Labeling and Enforcement Example

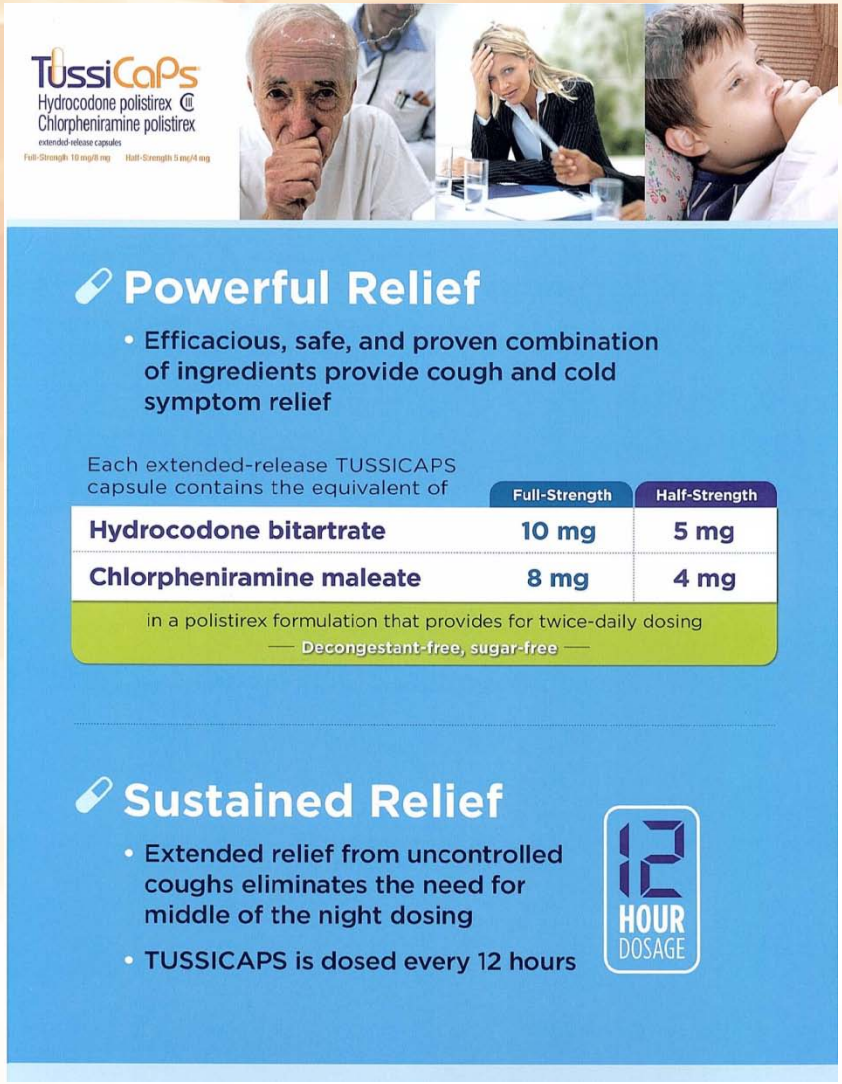
- TussiCaps is associated with drug abuse and dependence.
- Adverse Reactions: nausea and vomiting, sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes, and dose-related respiratory depression, which has been associated with death

TussiCaps® Product Labeling and Enforcement Example



- **Omission of material facts**
  - **For the relief of cough and upper respiratory symptoms associated with colds or allergies**
    - **Omission of “in adults and children 6 years of age and older”**

TussiCaps® Product Labeling and Enforcement Example



- Image of coughing young child
- Contraindicated in children < 6 years of age due to the risk of fatal respiratory depression
- PI also indicates that caution should be exercised when administering to pediatric patients ≥ 6 years of age

TussiCaps® Product Labeling and Enforcement Example

"This brochure is the property of ECR Pharmaceuticals and is to remain in the representative's possession. Appropriate product labeling should accompany discussion with the healthcare professionals and distribution of product samples."

TussiCaps® Product Labeling and Enforcement Example

- **Omission of Risk**
  - Fails to include **any** risk information despite numerous efficacy claims
  - Statements at the bottom of last page:
    - "This brochure is the property of ECR Pharmaceuticals and is to remain in the representative's possession. Appropriate product labeling should accompany discussions with the healthcare professionals and distribution of product samples."
    - This does not mitigate the omission of risk.
  - By failing to present any information regarding the risks, including serious and potentially fatal risks, the sales aid is misleading because it suggests that TussiCaps is safer than has been demonstrated, and is especially concerning in its potential impact on the public health.

Brovana® Product Labeling and Enforcement Example

- **Indication**
  - Long-term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA Inhalation Solution is for use by nebulization only.

- **Important Limitations of Use**
  - Brovana is not indicated to treat acute deteriorations of COPD.
  - Brovana is not indicated to treat asthma. The safety and effectiveness of Brovana in asthma have not been established.

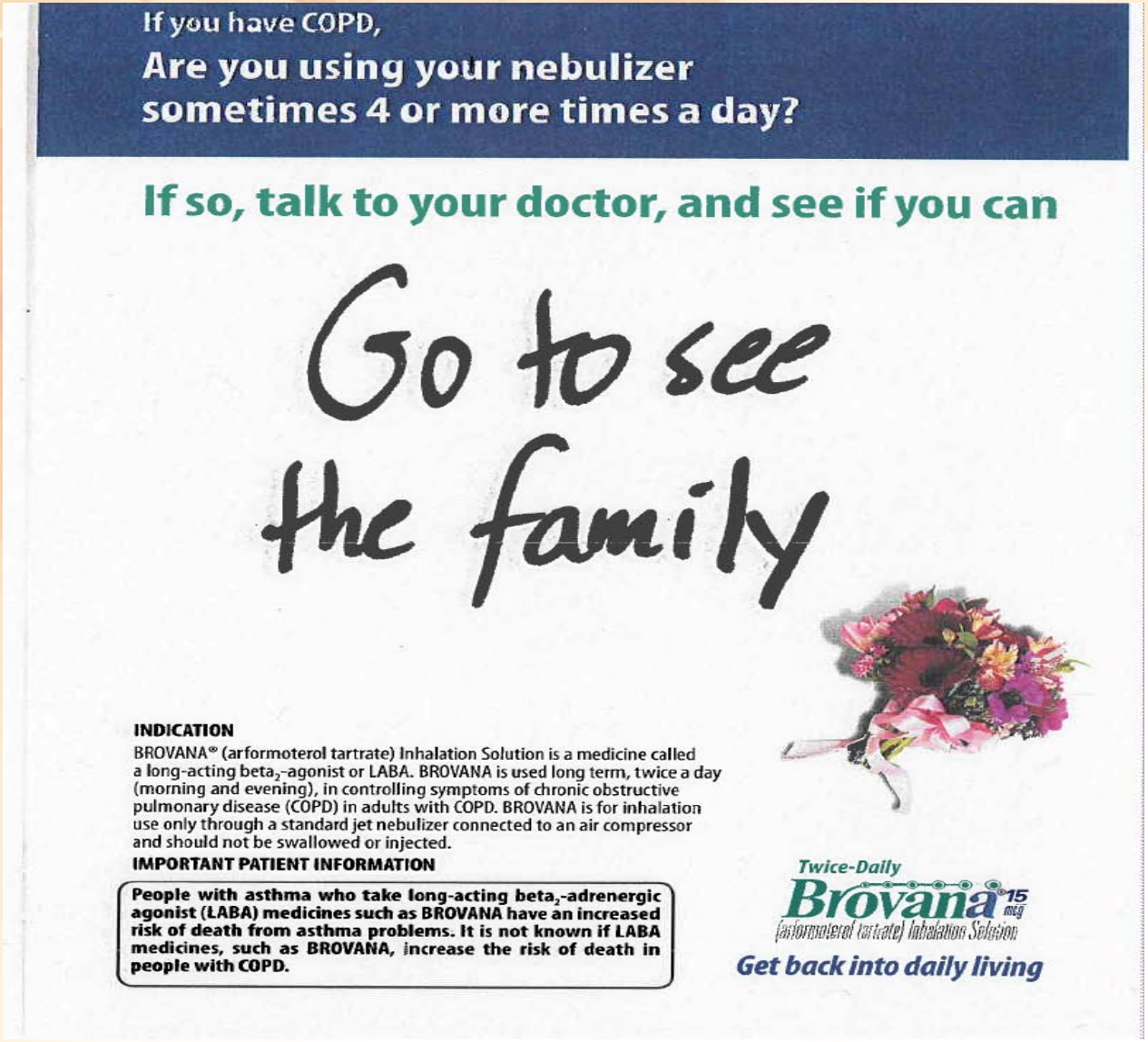
Brovana® Product Labeling and Enforcement Example

- **Boxed Warning**
  - Asthma-related death
- **Contraindications**
  - Patients with history of hypersensitivity to arformoterol, racemic formoterol, or to any other components of Brovana
  - Patients with asthma without the use of a long-term asthma control medication

Brovana® Product Labeling and Enforcement Example

- **Warnings and Precautions**
  - Deterioration of disease and acute episodes, excessive use of Brovana and use with other Long-Acting Beta2-Agonists (LABA), paradoxical bronchospasm, cardiovascular effects, coexisting conditions, hypokalemia and hyperglycemia, and immediate hypersensitivity reactions
- **Adverse Reactions (most common)**
  - Pain, chest pain, back pain, diarrhea, sinusitis, leg cramps, dyspnea, rash, flu syndrome, peripheral edema, and lung disorder

Brovana® Product Labeling and Enforcement Example



Notice of Violation

Patient Brochures

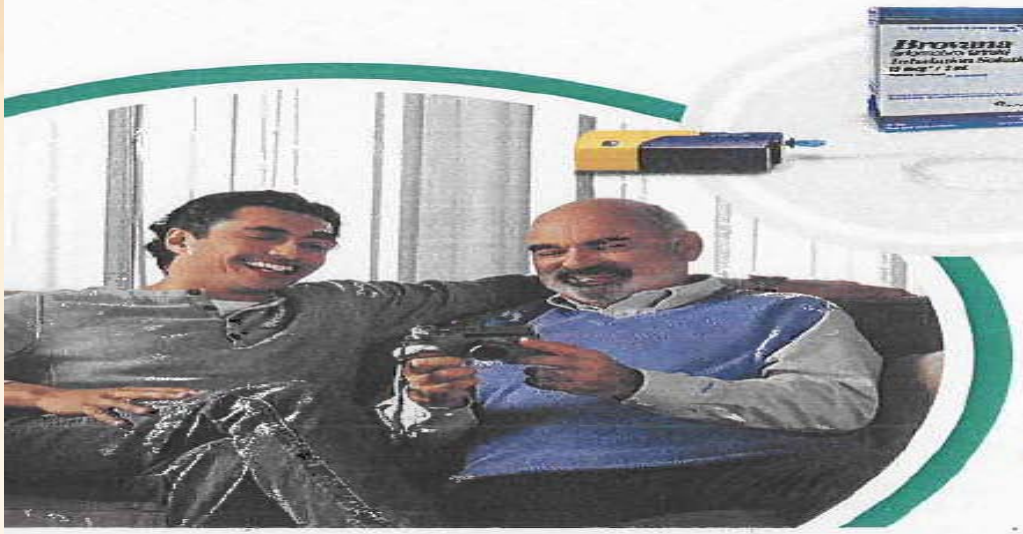
October 24, 2013

Brovana® Product Labeling and Enforcement Example

With the right COPD medicine, you may get back to daily living.

- **One dose of BROVANA®** (arformoterol tartrate) Inhalation Solution **may help you breathe better for up to 12 hours at a time**
- **BROVANA is taken twice a day—once in the morning and once in the evening**
- **BROVANA is taken with a nebulizer, a device that turns BROVANA into a fine mist that's easy to breathe**
- **It takes just 5 to 10 minutes to take a dose of BROVANA**
- **BROVANA is covered under Medicare Part B***

*No guarantee of coverage.



Nebulizer system and BROVANA are sold separately.

Twice-Daily
Brovana® 15 mcg
(arformoterol tartrate) Inhalation Solution
Get back into daily living

Brovana® Product Labeling and Enforcement Example

- **Overstatement the Efficacy**
  - Claims suggest that an outcome of treatment with Brovana is the ability for patients to resume their baseline activities of daily living.

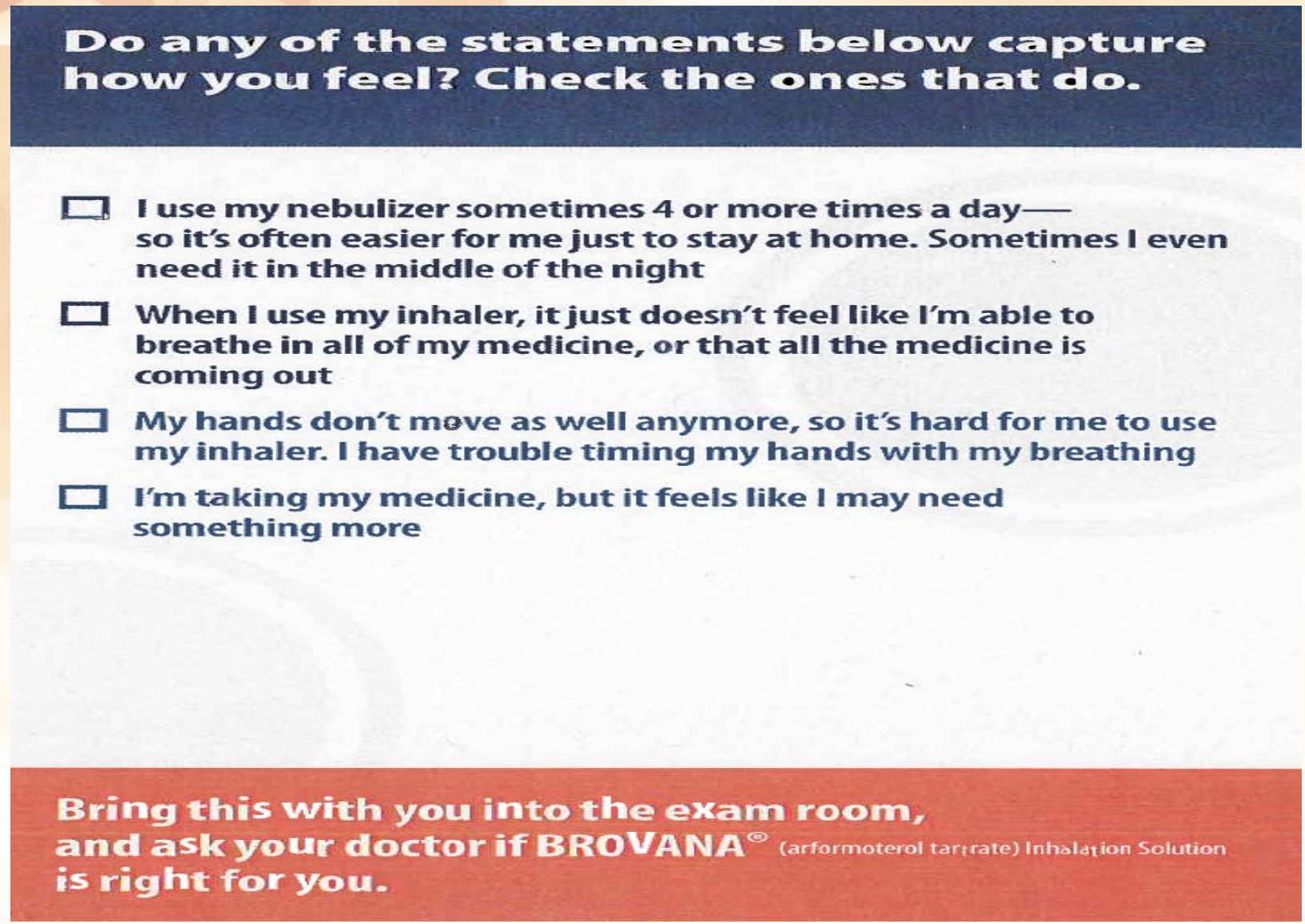
- **Clinical Studies**
  - BROVANA Inhalation Solution 15 mcg twice daily resulted in a statistically significant change of approximately 11% in mean forced expiratory volume in one second (FEV_1) (as measured by percent change from study baseline FEV1 at the end of the dosing interval over the 12 weeks of treatment, the primary efficacy endpoint) compared to placebo.

Brovana® Product Labeling and Enforcement Example

Patient Brochures Claims:

- "If you have COPD, **Are you using your nebulizer sometimes 4 or more times a day?**"
- "If you have COPD, **Do you feel you're just not able to breathe in all your medicine?**"
- "If you have COPD, **Is it hard for you to depress your inhaler and time your breaths to get your medicine out?**"
- "If you have COPD, **Do you take your medicine correctly, but still feel like you may need something more?**"

Brovana® Product Labeling and Enforcement Example



Brovana® Product Labeling and Enforcement Example

Unsubstantiated Superiority Claims

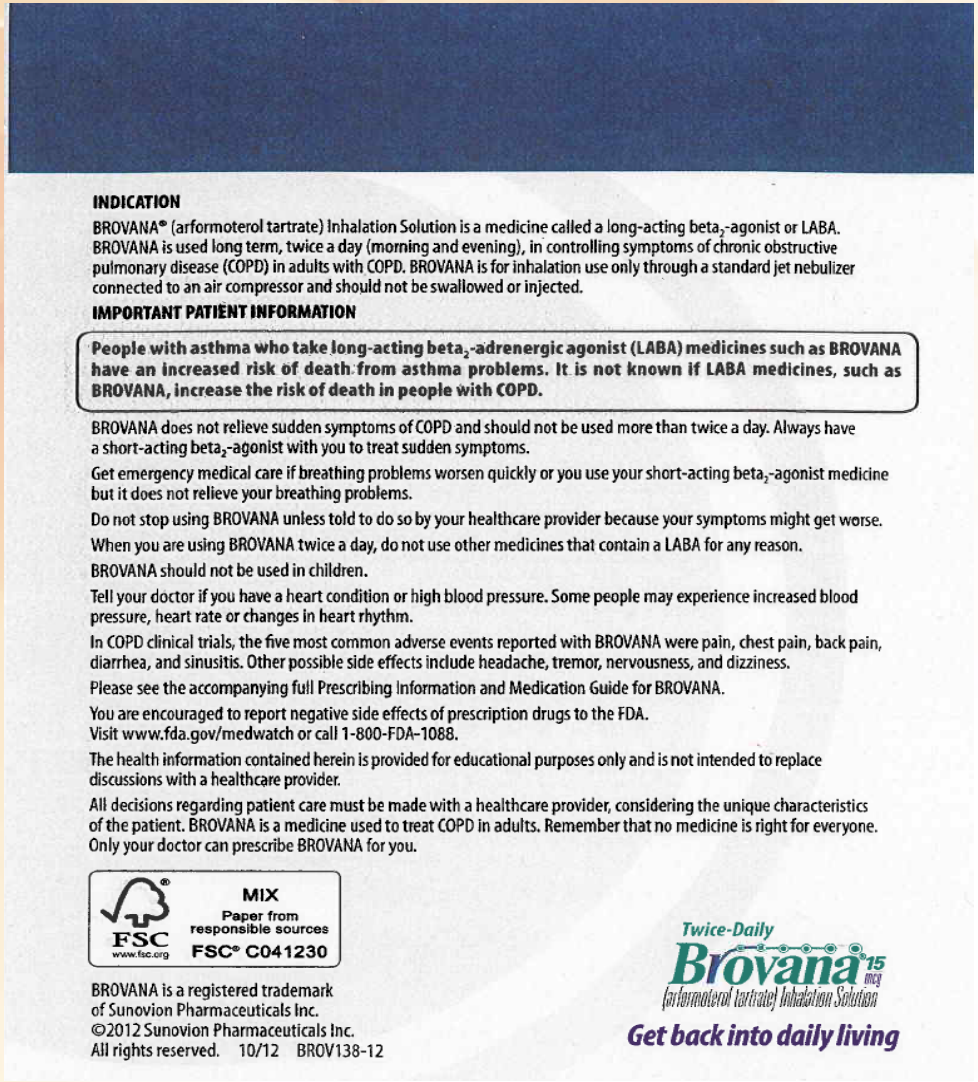
- Claims suggest that Brovana will be effective for those who have not had success with other COPD therapies based on Brovana's ability to overcome potential challenges associated with these therapies (e.g., therapies dosed ≥ 4 times/day or delivery system (e.g., DPIs or MDIs).

- **Clinical Studies**
  - Trials included an active comparator (salmeterol). However, studies were not designed to measure clinical superiority.

Brovana® Product Labeling and Enforcement Example

- **Unsubstantiated Claims**
  - Claims regarding the potential difficulty patients may encounter depressing an inhaler to administer therapy are misleading because they imply that patients with compromised manual dexterity will more easily be able to administer Brovana as compared to other COPD inhaler therapies.
  - Medication Guide includes lengthy directions for use.
  - In the absence of adequate evidence to demonstrate that patients with compromised manual dexterity are more easily able to administer Brovana as compared to other inhaled COPD therapies, the claims are misleading.

Brovana® Product Labeling and Enforcement Example



INDICATION

BROVANA® (arformoterol tartrate) Inhalation Solution is a medicine called a long-acting beta$_2$-agonist or LABA. BROVANA is used long term, twice a day (morning and evening), in controlling symptoms of chronic obstructive pulmonary disease (COPD) in adults with COPD. BROVANA is for inhalation use only through a standard jet nebulizer connected to an air compressor and should not be swallowed or injected.

IMPORTANT PATIENT INFORMATION

People with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines such as BROVANA have an increased risk of death from asthma problems. It is not known if LABA medicines, such as BROVANA, increase the risk of death in people with COPD.

BROVANA does not relieve sudden symptoms of COPD and should not be used more than twice a day. Always have a short-acting beta$_2$-agonist with you to treat sudden symptoms.

Get emergency medical care if breathing problems worsen quickly or you use your short-acting beta$_2$-agonist medicine but it does not relieve your breathing problems.

Do not stop using BROVANA unless told to do so by your healthcare provider because your symptoms might get worse.

When you are using BROVANA twice a day, do not use other medicines that contain a LABA for any reason.

BROVANA should not be used in children.

Tell your doctor if you have a heart condition or high blood pressure. Some people may experience increased blood pressure, heart rate or changes in heart rhythm.

In COPD clinical trials, the five most common adverse events reported with BROVANA were pain, chest pain, back pain, diarrhea, and sinusitis. Other possible side effects include headache, tremor, nervousness, and dizziness.

Please see the accompanying full Prescribing Information and Medication Guide for BROVANA.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

The health information contained herein is provided for educational purposes only and is not intended to replace discussions with a healthcare provider.

All decisions regarding patient care must be made with a healthcare provider, considering the unique characteristics of the patient. BROVANA is a medicine used to treat COPD in adults. Remember that no medicine is right for everyone. Only your doctor can prescribe BROVANA for you.

FSC www.fsc.org MIX Paper from responsible sources FSC® C041230

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All rights reserved. 10/12 BROV138-12

Twice-Daily Brovana 15 mcg (arformoterol tartrate) Inhalation Solution

Get back into daily living

- **Minimization of Risk**
  - Efficacy claims prominently presented in large, bolded font size and colorful text and graphics surrounded by a significant amount of white space
  - Risk information presented in small font, surrounded by little white space, and in single-spaced format

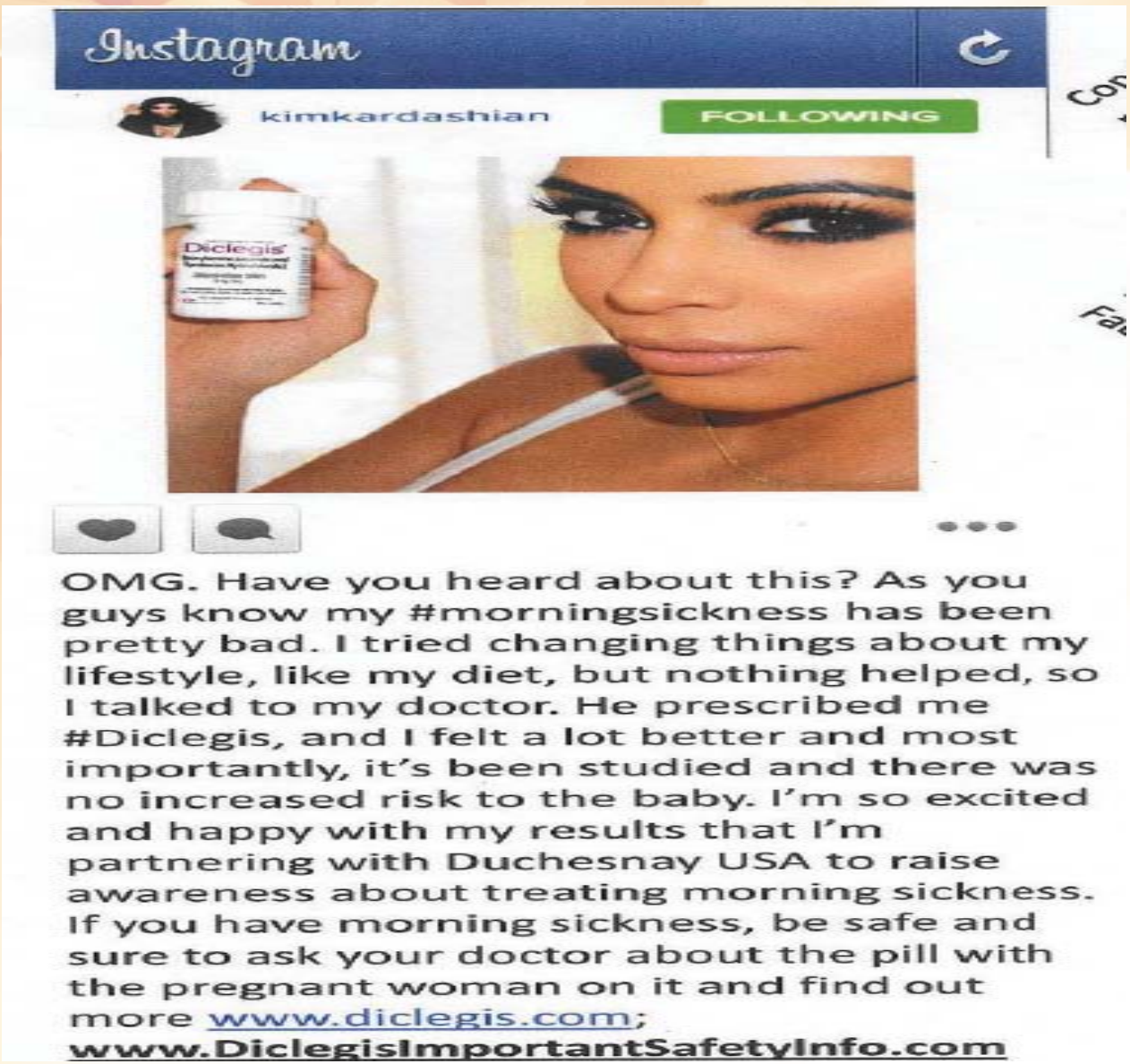
Diclegis Product Labeling and Enforcement Example

- **Indication**
  - For the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management
- **Limitations of Use**
  - DICLEGIS has not been studied in women with hyperemesis gravidarum.

Diclegis Product Labeling and Enforcement Example

- **Contraindications**
  - Women known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any inactive ingredient in the formulation, as well as in women who are taking monoamine oxidase inhibitors (MAOIs)
- **Warnings and Precautions**
  - Activities requiring mental alertness and concomitant medical conditions
- **Adverse reactions (most common)**
  - Somnolence

Diclegis Product Labeling and Enforcement Example



Warning Letter

Kim Kardashian
Social Media Post

August 7, 2015

Diclegis Product Labeling and Enforcement Example

- **Omission of Risk**
  - Presents various efficacy claims for Diclegis. However, it entirely omits all risk information.
  - Statements “[F]ind out more www.diclegis.com; www.DiclegisImportantSafetyInfo.com[,]” do not mitigate omission of risk.
- **Omission of Material Fact**
  - Failed to provide material information that Diclegis has not been studied in women with hyperemesis gravidarum

Diclegis Corrective

Instagram

Get the app Log in

kimkardashian FOLLOW

413k likes 3w

kimkardashian #CorrectiveAd I guess you saw the attention my last #morningsickness post received. The FDA has told Duchesnay, Inc., that my last post about Diclegis (doxylamine succinate and pyridoxine HCl) was incomplete because it did not include any risk information or important limitations of use for Diclegis. A link to this information accompanied the post, but this didn't meet FDA requirements. So, I'm re-posting and sharing this important information about Diclegis. For US Residents Only.
Diclegis is a prescription medicine used to treat nausea and vomiting of pregnancy in women who have not improved with change in diet or other non-medicine treatments.
Limitation of Use: Diclegis has not been studied in women with hyperemesis gravidarum.

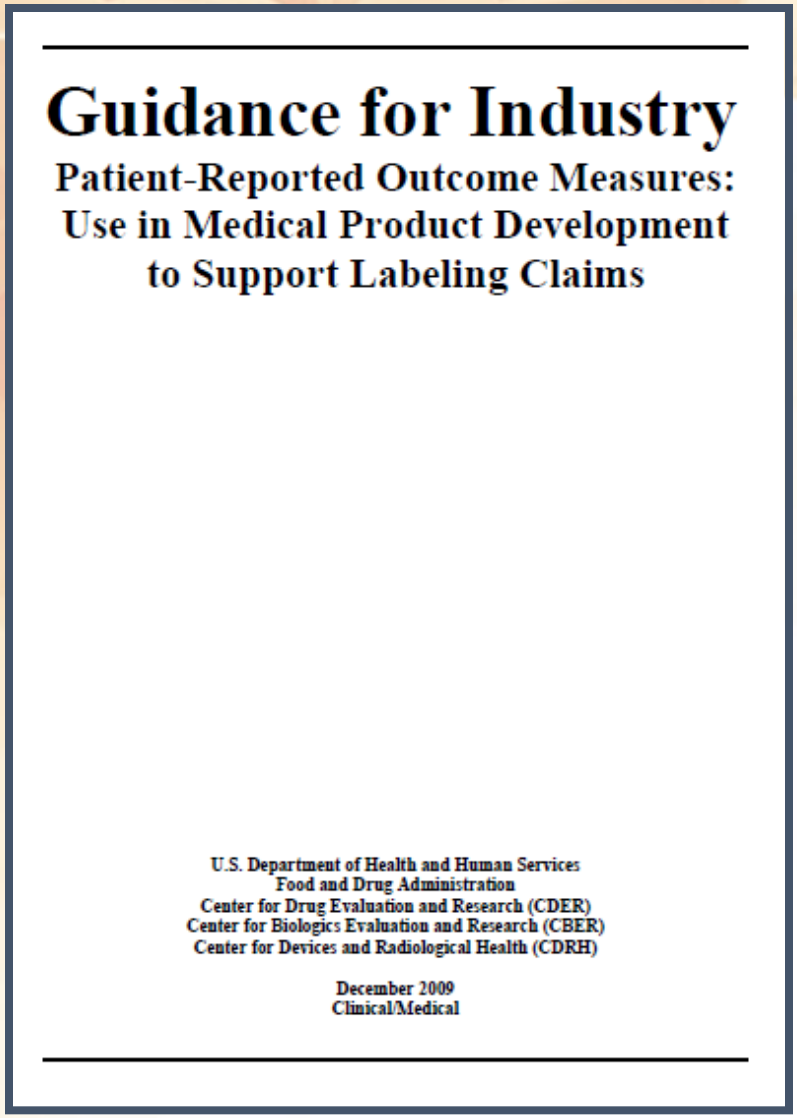
Log in to like or comment. ooo

Clinical Outcome Assessment (COA) Promotional Claims

COA: any assessment that may be influenced by human choices, judgment, or motivation and may either support direct or indirect evidence of treatment benefit.

- **Patient-reported outcomes (PROs)**
- **Clinician-reported outcomes (ClinROs)**
- **Observer-reported outcomes (ObsROs)**
- **Performance outcomes (PerfOs)**

Clinical Outcome Assessment (COA) Promotional Claims



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

- Serves as the “gold standard” for good measurement principles for any COA
- Outlines how the FDA interprets “well-defined and reliable” measures intended to provide evidence of treatment benefit

Clinical Outcome Assessment (COA) Promotional Claims

General Considerations with COAs:

- In general, the **same** study principles that apply to other clinical endpoint measures apply to reported assessments (PROs, ClinROs, and ObsROs).
  - Should be designated as **primary** or **key secondary** endpoints
- Instruments for reported assessments need to be **well-defined** and **reliable** in the clinical trial context of use.
  - **Content validity** of instruments need to be established

Clinical Outcome Assessment (COA) Promotional Claims

Labeling Example:

Approved Product Labeling for Jakafi™

(ruxolitinib), tablets for oral use

November 2011

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JAKAFI safely and effectively. See full prescribing information for JAKAFI.

JAKAFI™ (ruxolitinib) tablets, for oral use
Initial U.S. Approval: 2011

INDICATIONS AND USAGE

Jakafi is a kinase inhibitor indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. (1)

DOSAGE AND ADMINISTRATION

- The starting dose of Jakafi is 20 mg given orally twice daily for patients with a platelet count greater than 200 X 10^9/L, and 15 mg twice daily for patients with a platelet count between 100 X 10^9/L and 200 X 10^9/L. (2.1)
- Perform a complete blood count before initiating therapy with Jakafi. Monitor complete blood counts every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Modify dose for thrombocytopenia. (2.1) (2.2)
- Increase dose based on response and as recommended to a maximum of 25 mg twice daily. Discontinue after 6 months if no spleen reduction or symptom improvement (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg, 15 mg, 20 mg and 25 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Thrombocytopenia, anemia and neutropenia can occur. Manage by dose reduction, or interruption or transfusion. (5.1)

Clinical Outcome Assessment (COA) Promotional Claims

Jakafi™ Labeling Example:

Clinical Studies:

- The primary efficacy endpoint was the proportion of pts achieving ≥ 35% reduction from baseline in spleen volume at Week 24 (measured by MRI or CT).
- A key secondary endpoint was the proportion of pts with a >50% reduction in Total Symptom Score from baseline to Week 24, as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary.

Clinical Outcome Assessment (COA) Promotional Claims

Jakafi™ Labeling Example:

Instrument:

- The MFSAF is a daily diary that captures the core symptoms of myelofibrosis (abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain, and early satiety).

- Symptom scores range from 0 (no symptoms) to 10 (“worst imaginable” symptoms). The scores were added to create the daily total score (maximum=60).

Clinical Outcome Assessment (COA) Promotional Claims

Jakafi™ Labeling Example:

Results:

- A higher proportion of pts in the Jakafi group had a 50% or greater reduction in Total Symptom Score than in the placebo group, with a median time to response of <4 weeks.

Table 7: Improvement in Total Symptom Score

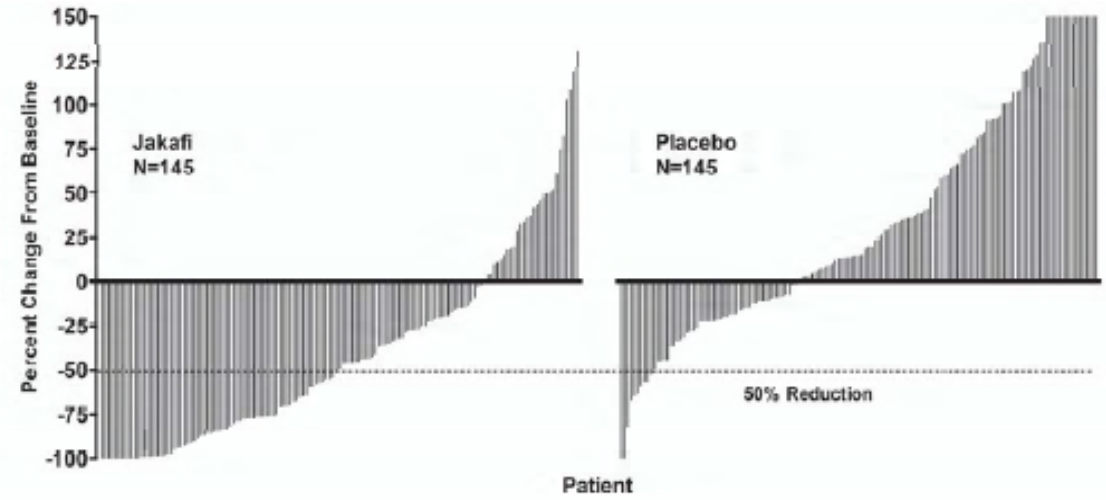
	Jakafi (N=148)	Placebo (N=152)
Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24	68 (45.9)	8 (5.3)
P-value	< 0.0001	

Clinical Outcome Assessment (COA) Promotional Claims

Jakafi™ Labeling Example:

Figure 2 shows the percent change from baseline in Total Symptom Score for each patient at Week 24 (Jakafi N=129, placebo N=103) or the last evaluation on randomized therapy prior to Week 24 for patients who did not complete 24 weeks of randomized treatment (Jakafi N=16, placebo N=42). Results are excluded for 5 patients with a baseline Total Symptom Score of zero, 8 patients with missing baseline and 6 patients with insufficient post-baseline data.

Figure 2: Percent Change from Baseline in Total Symptom Score at Week 24 or Last Observation for Each Patient (Study 1)



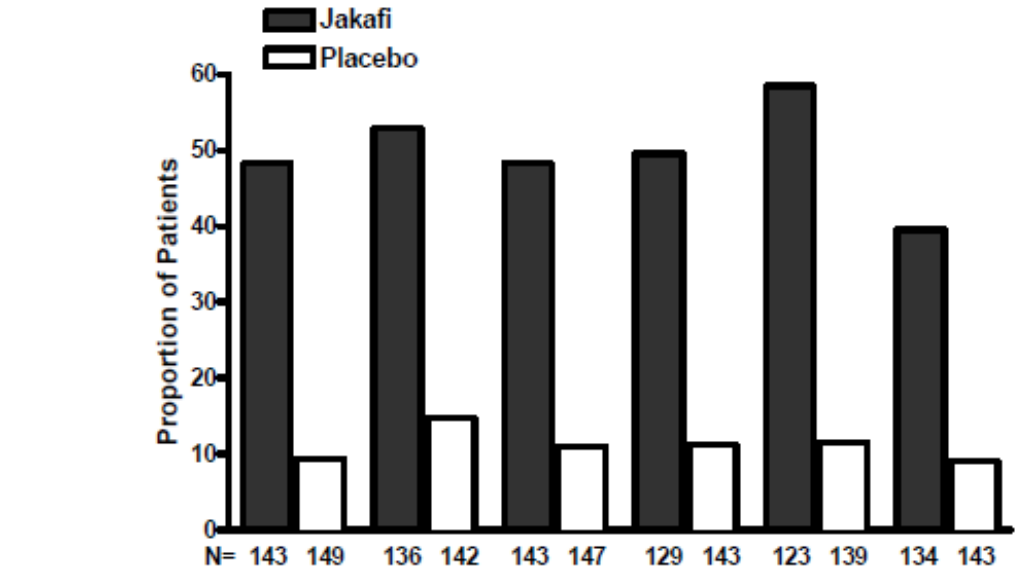
Worsening of Total Symptom Score is truncated at 150%.

Clinical Outcome Assessment (COA) Promotional Claims

Jakafi™ Labeling Example:

This figure indicates that all 6 of the symptoms contributed to the higher Total Symptom Score response rate in the Jakafi group.

Figure 3: Proportion of Patients With 50% or Greater Reduction in Individual Symptom Scores at Week 24



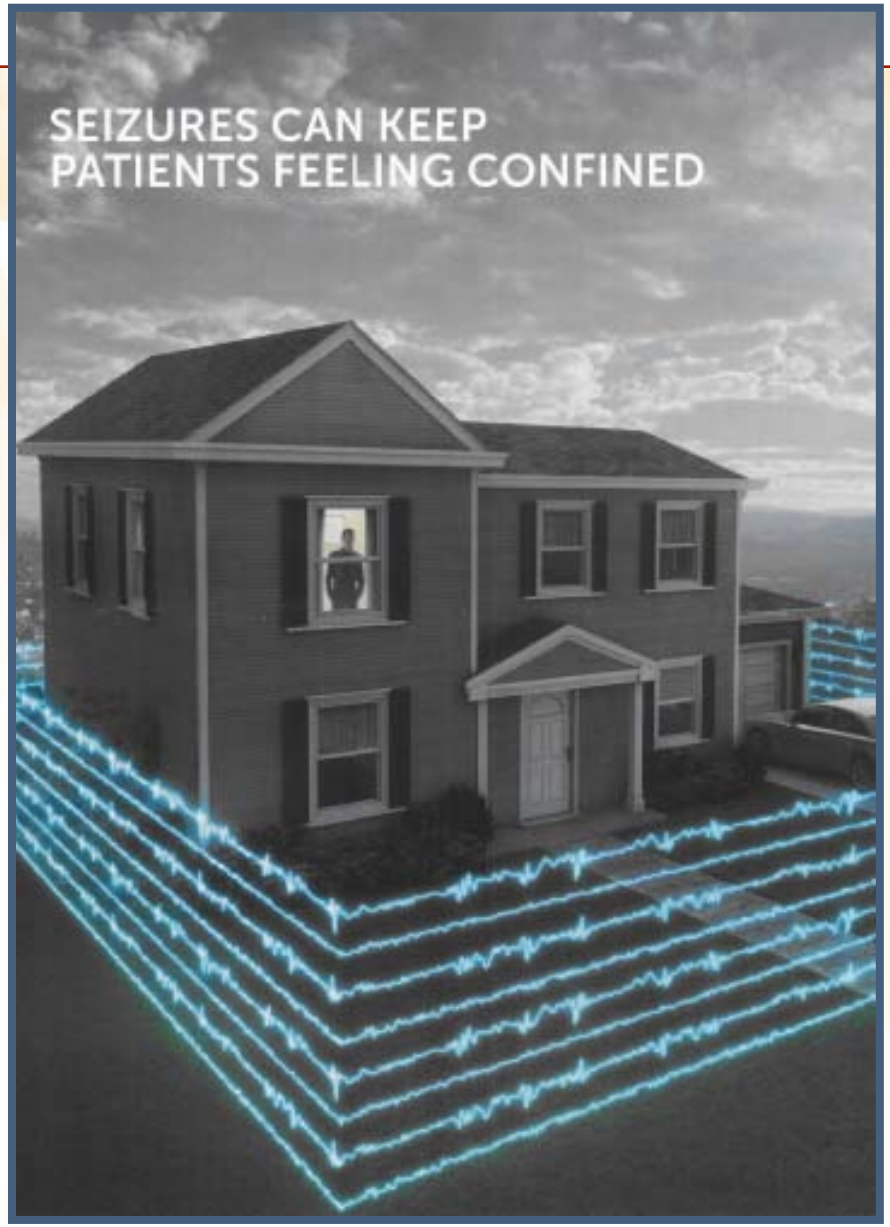
Individual score range = 0 to 10

Enforcement Examples with COA Claims

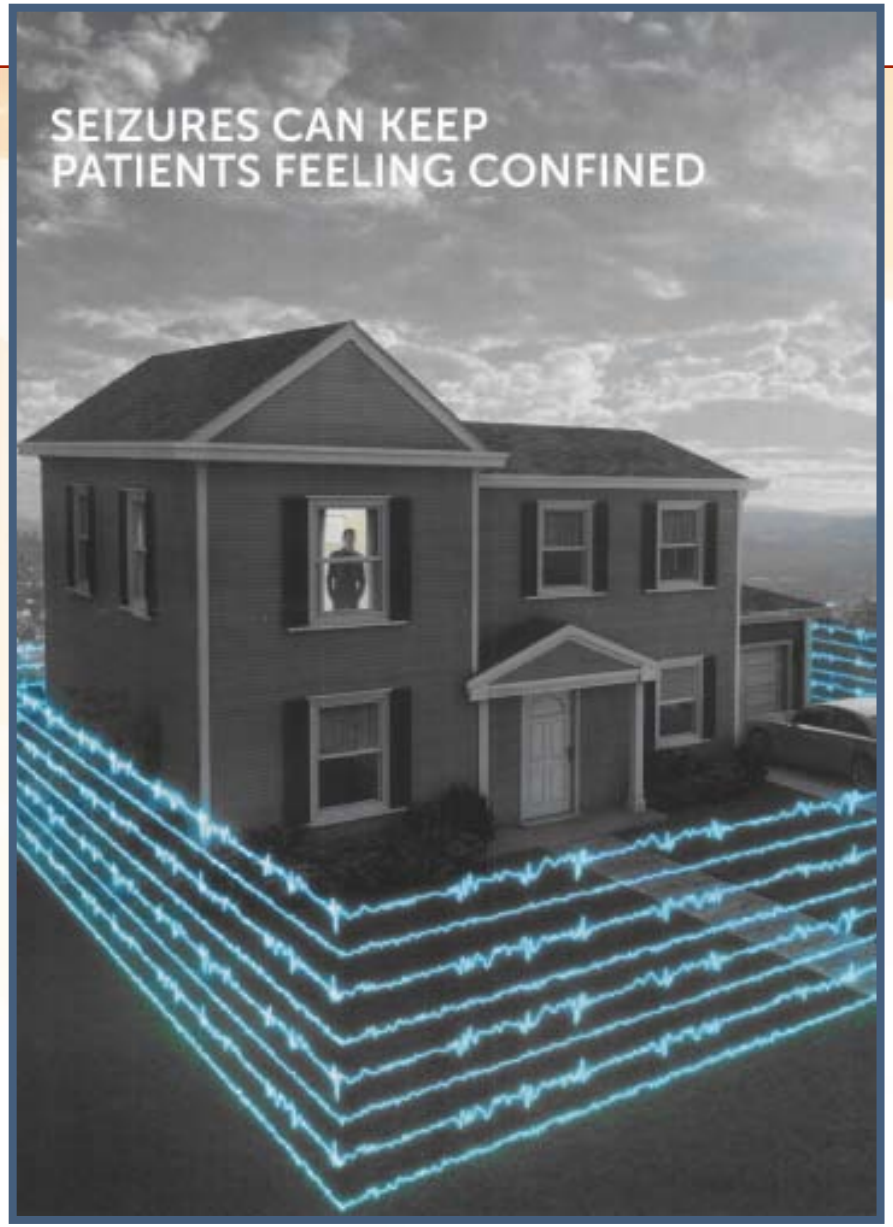
Notice of Violation:

Aptiom®
(eslicarbazepine acetate) Tablets

December 15, 2014



Enforcement Examples with COA Claims



Enforcement Examples with COA Claims

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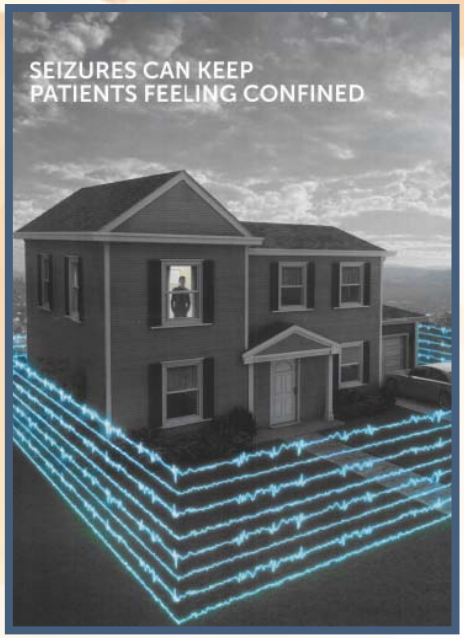

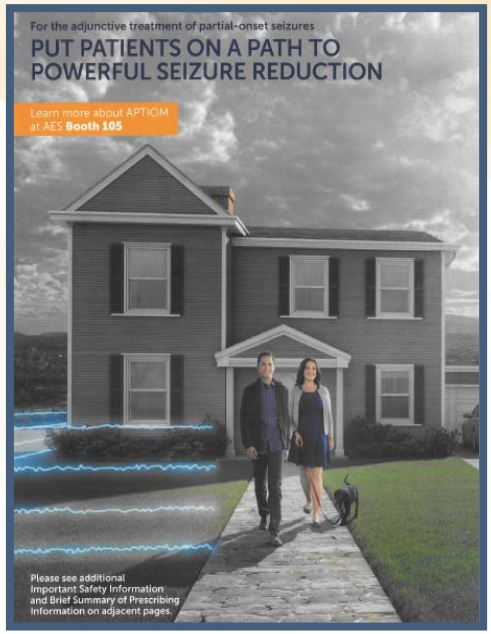

"The claims and presentations misleadingly overstate the efficacy of Aptiom by suggesting that the drug has been shown to have treatment benefits on patients' feelings of confinement associated with seizures."

Enforcement Examples with COA Claims

Aptiom Labeling (Sec 14 CLINICAL STUDIES):

Table 4: Standardized Seizure Frequency During the Maintenance Phase Over 28 Days and Percent Reduction from Baseline in Seizure Frequency

	Placebo	APTIOM	
		800 mg	1200 mg
Study 3			
N	95	88	87
Seizure Frequency (LS Mean seizures per 28 days) (p-value)	6.6	5.0 (0.047*)	4.3 (0.001*)
Median Percent Reduction from Baseline in Seizure Frequency (%)	-15	-36	-39
Study 4			
N	99	87	81
Seizure Frequency (LS Mean seizures per 28 days) (p-value)	8.6	6.2 (0.006*)	6.6 (0.042*)
Median Percent Reduction from Baseline in Seizure Frequency (%)	-6	-33	-28
Study 5			
N	212	200	184
Seizure Frequency (LS Mean seizures per 28 days) (p-value)	7.9	6.5 (0.058)	6.0 (0.004*)
Median Percent Reduction from Baseline in Seizure Frequency (%)	-22	-30	-36

*statistically significant compared to placebo

Enforcement Examples with COA Claims

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		800 mg	1200 mg
Study 3			
N	95	88	87
Seizure Frequency (LS Mean seizures per 28 days) (p-value)	6.6	5.0 (0.047*)	4.3 (0.001*)
Median Percent Reduction from Baseline in Seizure Frequency (%)	-15	-36	-39
Study 4			
N	99	87	81
Seizure Frequency (LS Mean seizures per 28 days) (p-value)	8.6	6.2 (0.006*)	6.6 (0.042*)
Median Percent Reduction from Baseline in Seizure Frequency (%)	-6	-33	-28
Study 5			
N	212	200	184
Seizure Frequency (LS Mean seizures per 28 days) (p-value)	7.9	6.5 (0.058)	6.0 (0.004*)
Median Percent Reduction from Baseline in Seizure Frequency (%)	-22	-30	-36

*statistically significant compared to placebo

- "Although Aptiom may reduce seizure frequency, FDA is not aware of substantial evidence demonstrating any effectiveness of Aptiom on patients' feelings on confinement associated with seizures."
- No patient-reported data in the labeling

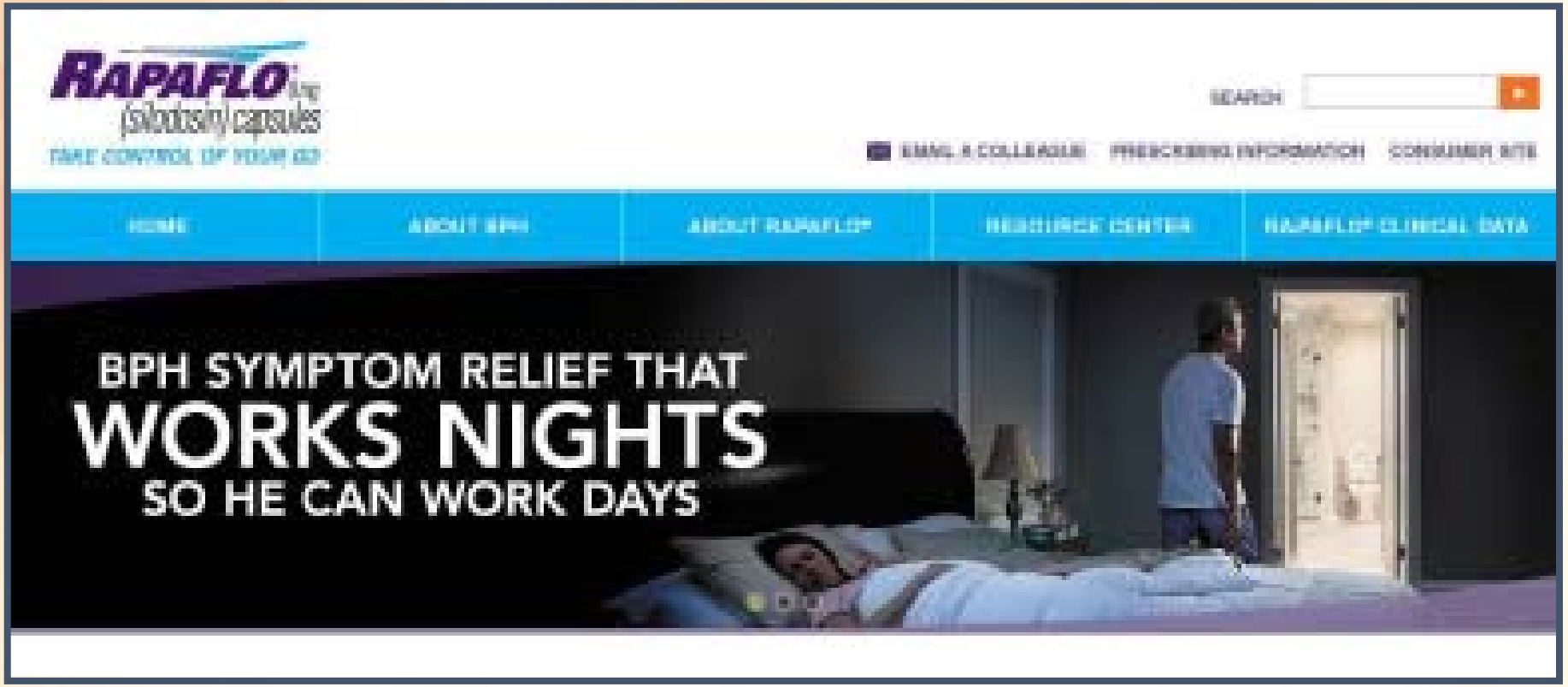
Enforcement Examples with COA Claims

Notice of Violation:

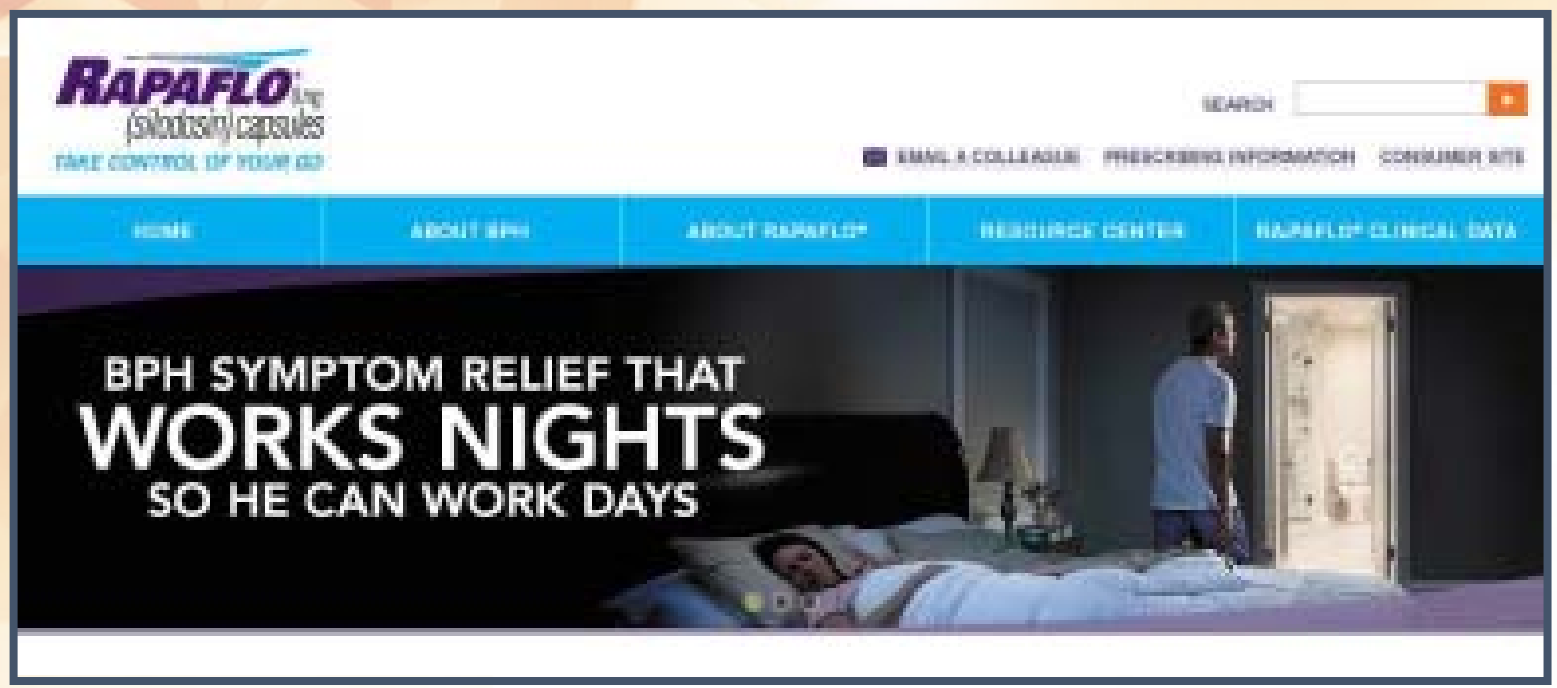
Rapaflo® (silodosin)
Capsule for oral use

May 19, 2015

Enforcement Examples with COA Claims



Enforcement Examples with COA Claims



The presentation is misleading because it “implies that in addition to improving BPH symptoms, Rapaflo has also been shown to improve both sleep disturbance (i.e., quality of sleep) and work productivity.”

Enforcement Examples with COA Claims

Rapaflo Labeling (Sec 14 CLINICAL STUDIES):

14.1 Benign Prostatic Hyperplasia

Two 12-week, randomized, double-blind, placebo-controlled, multicenter studies were conducted with 8 mg daily of silodosin. In these two studies, 923 patients [mean age 64.6 years; Caucasian (89.3%), Hispanic (4.9%), Black (3.9%), Asian (1.2%), Other (0.8%)] were randomized and 466 patients received RAPAFLO 8 mg daily. The two studies were identical in design except for the inclusion of pharmacokinetic sampling in Study 1. The primary efficacy assessment was the International Prostate Symptom Score (IPSS) which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms. Maximum urine flow rate (Qmax) was a secondary efficacy measure.

Enforcement Examples with COA Claims

Rapaflo Labeling (Sec 14 CLINICAL STUDIES):

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Two 12-week, randomized, double-blind, placebo-controlled, multicenter studies were conducted with 8 mg daily of silodosin. In these two studies, 923 patients [mean age 64.6 years; Caucasian (89.3%), Hispanic (4.9%), Black (3.9%), Asian (1.2%), Other (0.8%)] were randomized and 466 patients received RAPAFLO 8 mg daily. The two studies were identical in design except for the inclusion of pharmacokinetic sampling in Study 1. The primary efficacy assessment was the International Prostate Symptom Score (IPSS) which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms. Maximum urine flow rate (Qmax) was a secondary efficacy measure.

Enforcement Examples with COA Claims

Rapaflo Labeling (Sec 14 CLINICAL STUDIES):

in design except for the inclusion of pharmacokinetic sampling in Study 1. The primary efficacy assessment was the International Prostate Symptom Score (IPSS) which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms. Maximum urine flow rate (Qmax) was a secondary efficacy measure.

- "These studies did not measure the impact of treatment on individual symptoms, such as nocturia. Therefore, efficacy claims and presentations for Rapaflo that suggest improvement in one of the IPSS subscore symptoms (i.e., nocturia) are not supported by substantial evidence."

- "Moreover, the pivotal studies did not evaluate the impact of Rapaflo on quality of sleep or work productivity."

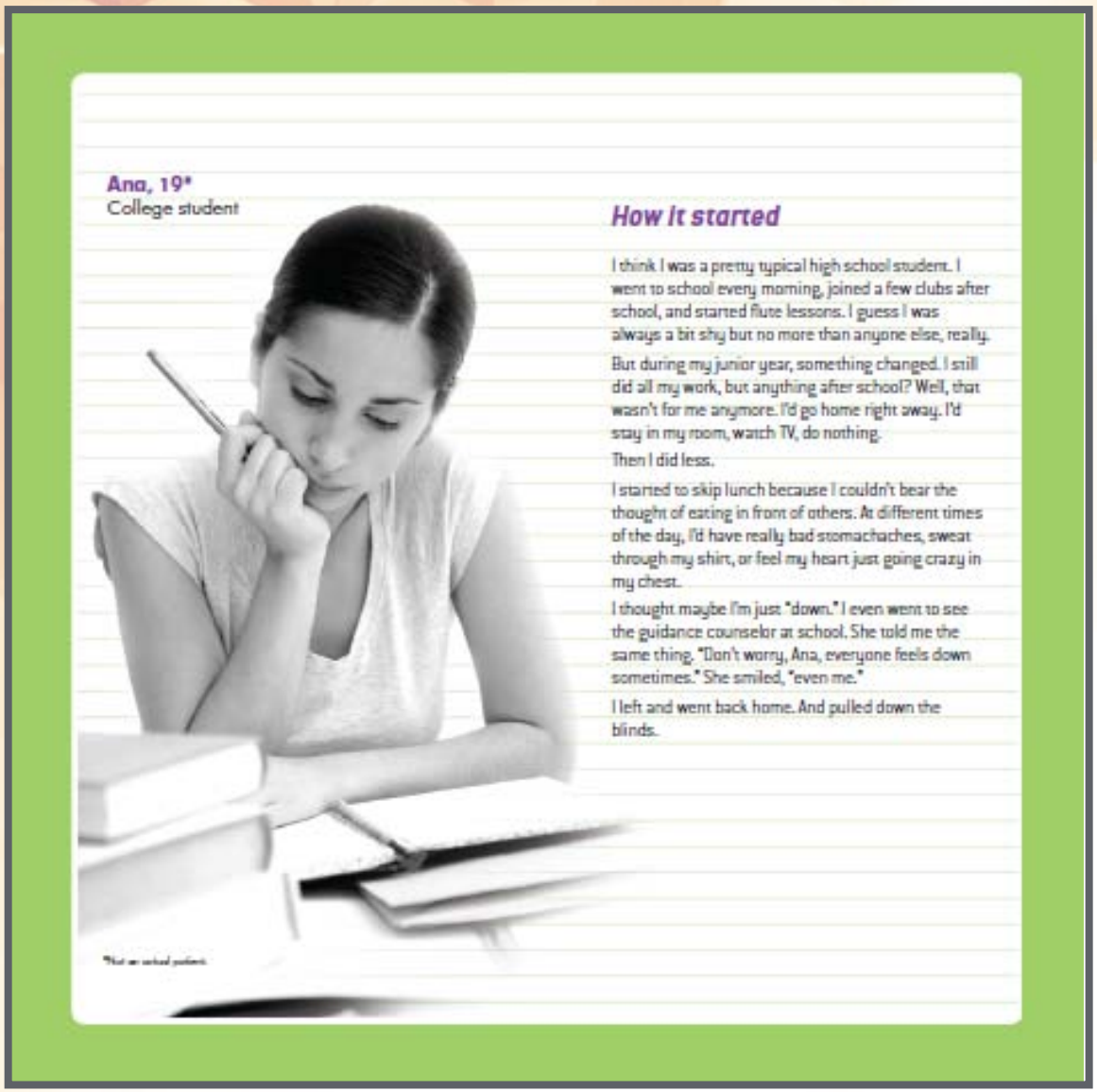
Enforcement Examples with COA Claims

Warning Letter:

Luvox CR®
(fluvoxamine maleate)
Extended-Release
Capsules

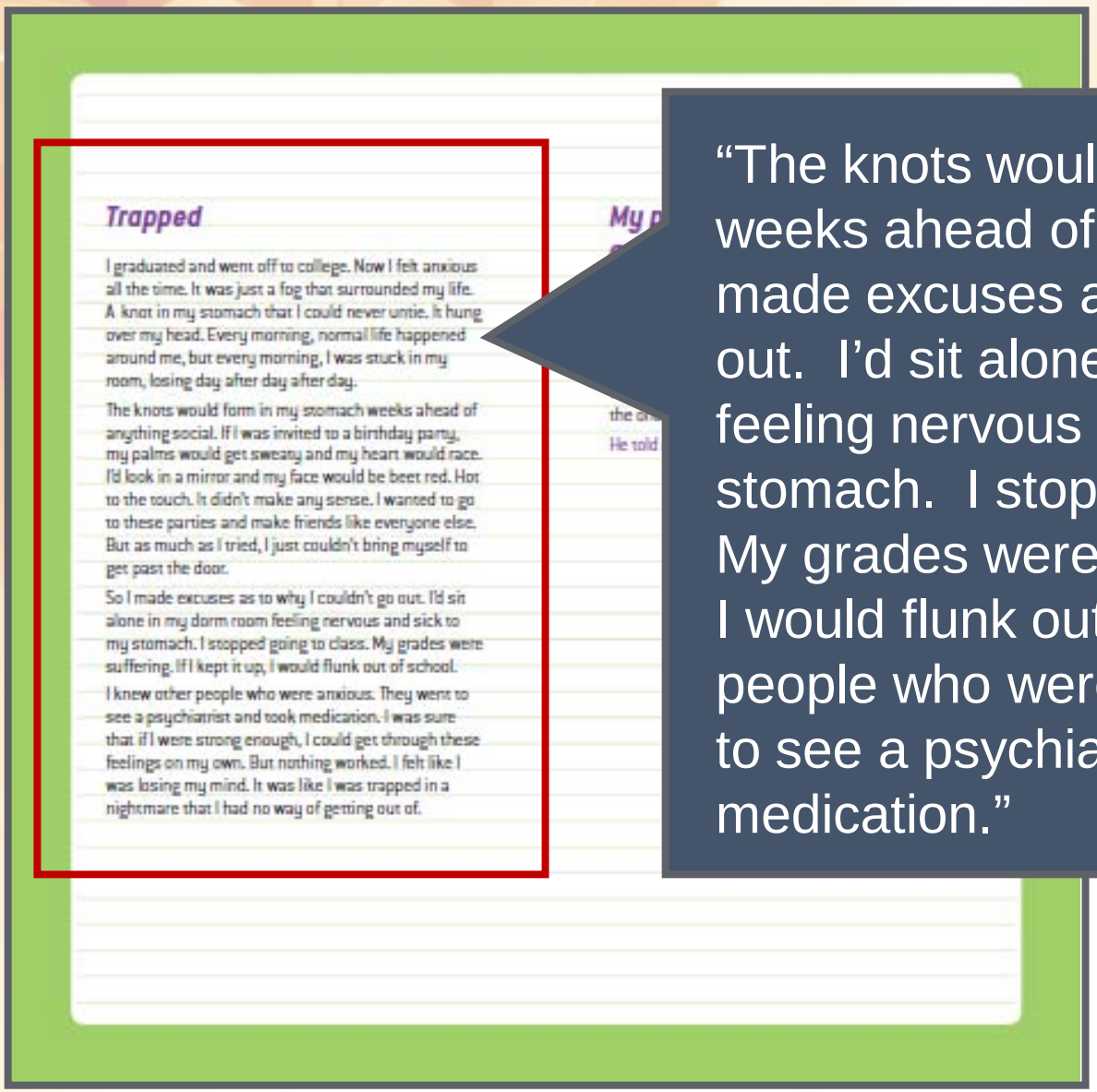
July 6, 2010

Enforcement Examples with COA Claims



The patient brochure includes a patient profile for Ana, a 19-year-old college student.

Enforcement Examples with COA Claims



Trapped

I graduated and went off to college. Now I felt anxious all the time. It was just a fog that surrounded my life. A knot in my stomach that I could never untie. It hung over my head. Every morning, normal life happened around me, but every morning, I was stuck in my room, losing day after day after day.

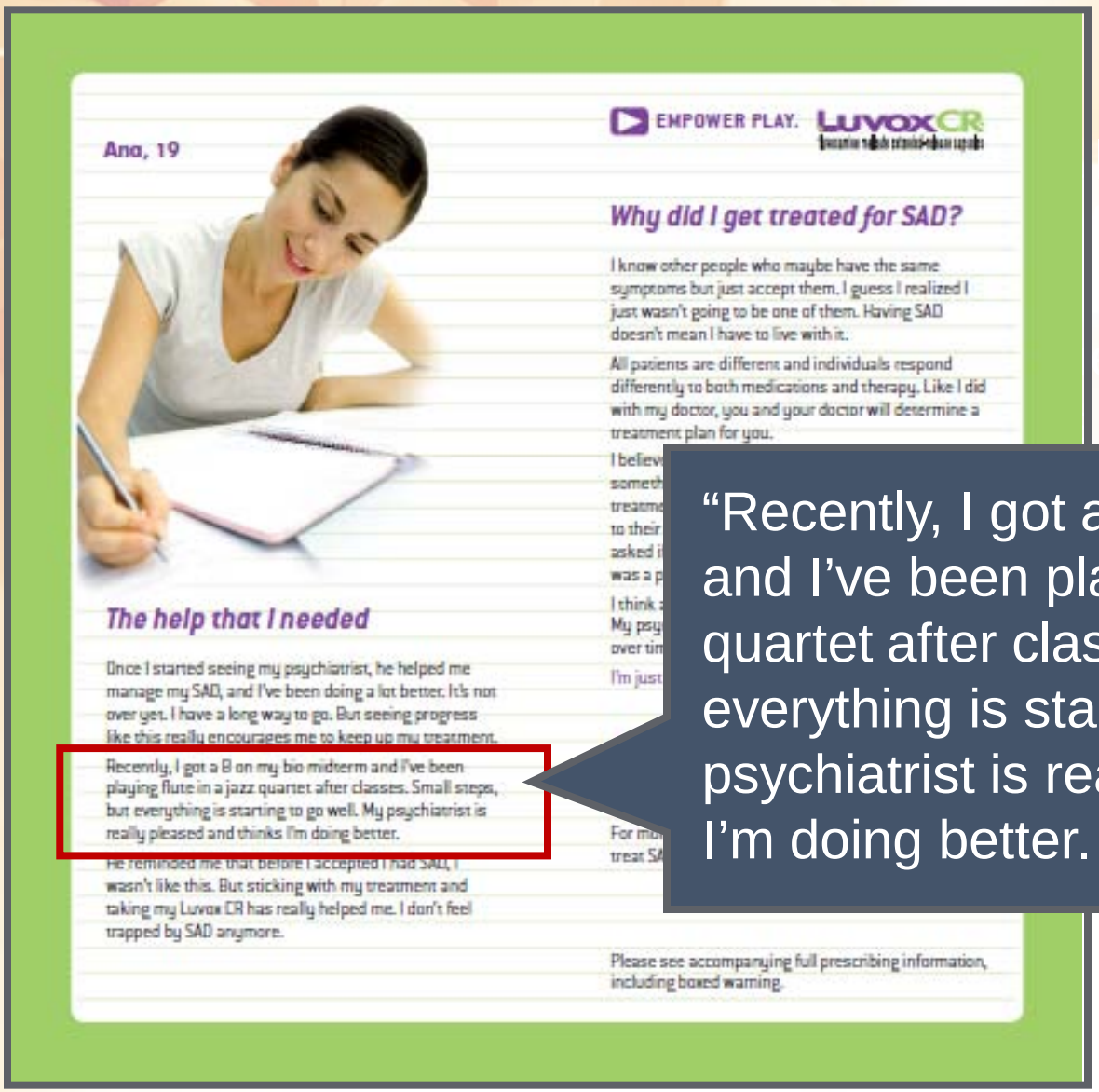
The knots would form in my stomach weeks ahead of anything social. If I was invited to a birthday party, my palms would get sweaty and my heart would race. I'd look in a mirror and my face would be beet red. Hot to the touch. It didn't make any sense. I wanted to go to these parties and make friends like everyone else. But as much as I tried, I just couldn't bring myself to get past the door.

So I made excuses as to why I couldn't go out. I'd sit alone in my dorm room feeling nervous and sick to my stomach. I stopped going to class. My grades were suffering. If I kept it up, I would flunk out of school.

I knew other people who were anxious. They went to see a psychiatrist and took medication. I was sure that if I were strong enough, I could get through these feelings on my own. But nothing worked. I felt like I was losing my mind. It was like I was trapped in a nightmare that I had no way of getting out of.

"The knots would form in my stomach weeks ahead of anything social...So I made excuses as to why I couldn't go out. I'd sit alone in my dorm room feeling nervous and sick to my stomach. I stopped going to class. My grades were suffering. If it kept up, I would flunk out of school. I knew other people who were anxious. They went to see a psychiatrist and took medication."

Enforcement Examples with COA Claims



Ana, 19

EMPOWER PLAY. LUVOX CR

Why did I get treated for SAD?

I know other people who maybe have the same symptoms but just accept them. I guess I realized I just wasn't going to be one of them. Having SAD doesn't mean I have to live with it.

All patients are different and individuals respond differently to both medications and therapy. Like I did with my doctor, you and your doctor will determine a treatment plan for you.

The help that I needed

Once I started seeing my psychiatrist, he helped me manage my SAD, and I've been doing a lot better. It's not over yet. I have a long way to go. But seeing progress like this really encourages me to keep up my treatment.

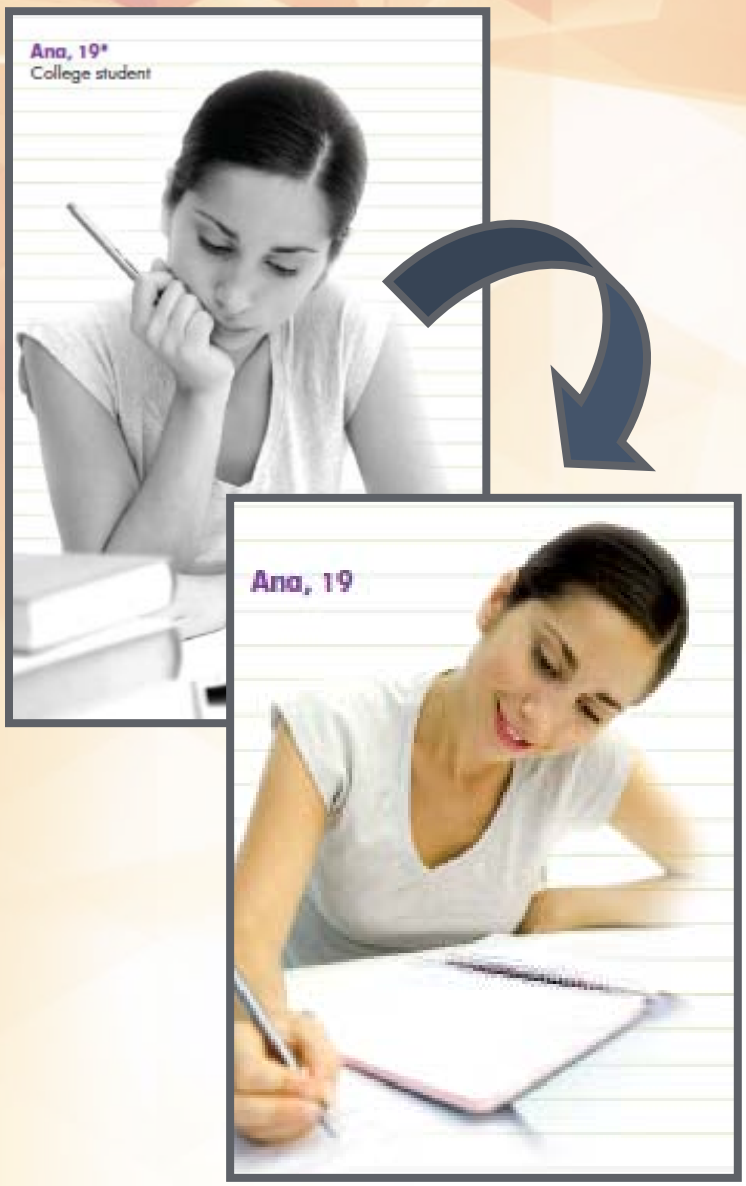
Recently, I got a B on my bio midterm and I've been playing flute in a jazz quartet after classes. Small steps, but everything is starting to go well. My psychiatrist is really pleased and thinks I'm doing better.

He reminded me that before I accepted I had SAD, I wasn't like this. But sticking with my treatment and taking my Luvox CR has really helped me. I don't feel trapped by SAD anymore.

Please see accompanying full prescribing information, including boxed warning.

"Recently, I got a B on my bio midterm and I've been playing flute in a jazz quartet after classes. Small steps, but everything is starting to go well. My psychiatrist is really pleased and thinks I'm doing better.

Enforcement Examples with COA Claims



"The overall impression created by these presentations is that the treatment with Luvox CR will markedly improve a patient's social functioning and academic performance…We are not aware of substantial evidence or substantial clinical experience to support the implication that patients treated with Luvox CR will experience such improvements in social functioning or academic performance."

Enforcement Examples with COA Claims

Luvox CR Labeling (CLINICAL PHARMACOLOGY):

Clinical Trials

Social Anxiety Disorder: The effectiveness of LUVOX CR Capsules in the treatment of social anxiety disorder was demonstrated in two 12-week, multicenter, placebo-controlled studies of adult outpatients with social anxiety disorder (DSM-IV). Patients in these trials were titrated in 50 mg increments over the first six weeks of the study on the basis of response and tolerance from a dose of 100 mg/day to a fluvoxamine maleate dose within a range of 100 mg to 300 mg once-a-day.

In these studies, the effectiveness of LUVOX CR Capsules compared to placebo was evaluated on the basis of change from baseline in the Liebowitz Social Anxiety Scale (LSAS). LUVOX CR Capsules demonstrated statistically significant superiority over placebo at the primary endpoint (Week 12) as assessed by the LSAS total score in both studies.

Enforcement Examples with COA Claims

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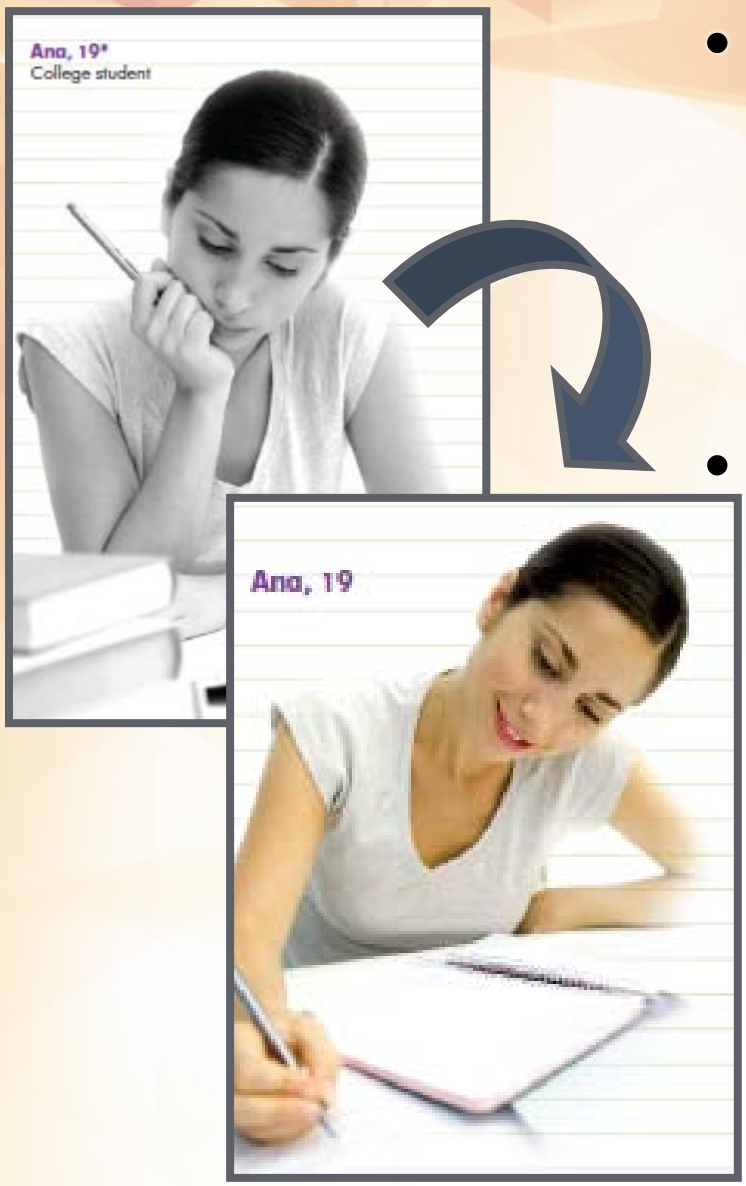
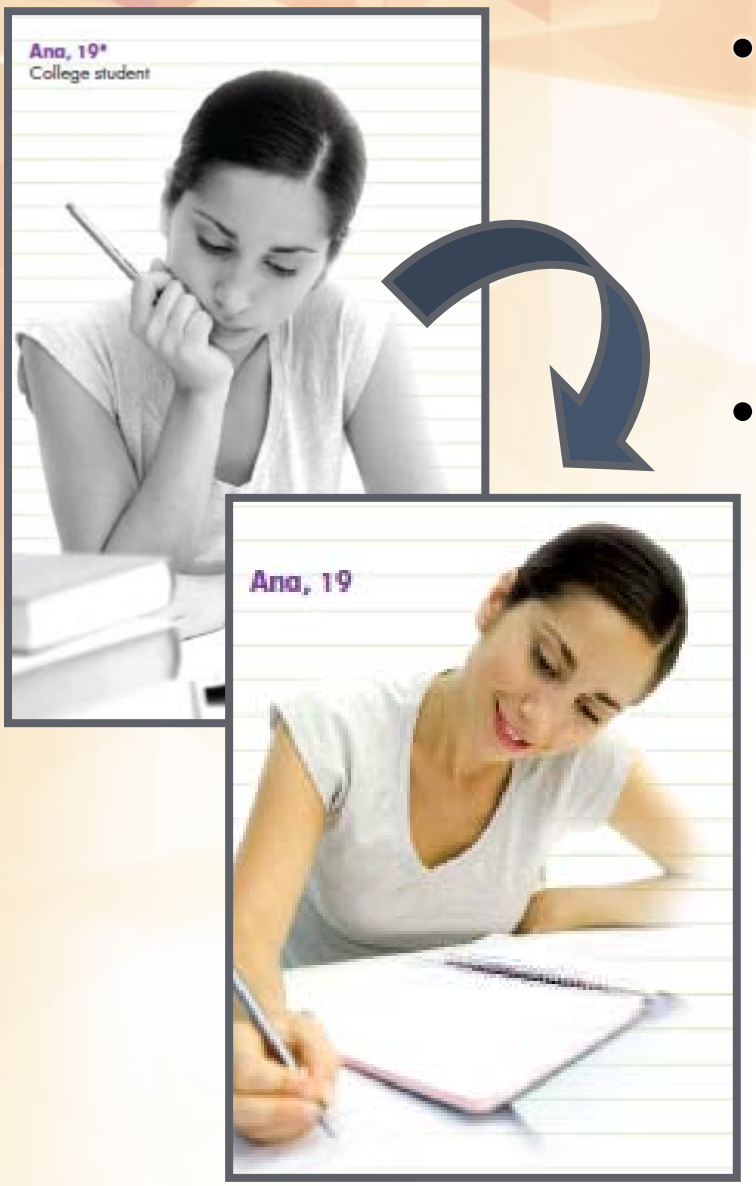
Enforcement Examples with COA Claims



- Luvox CR has been shown to improve **<u>total</u>** scores in the Liebowitz Social Anxiety Scale (LSAS) at Week 12.
- The LSAS includes 6 subscales and 24 items:
  - Subscales include: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance

Enforcement Examples with COA Claims



- The LSAS does not measure the impact of treatment on the 6 **individual** subscales or the 24 **individual** items.
- Clinical trial results showed improvements of **13.4** and **8.4** in total LSAS scores:
  - Scoring scale is in 15-point increments (moderate [55-65], marked [65-80], severe [80-95], very severe [>95])
  - No evidence that these improvements in LSAS scores correlate with the drastic improvements claimed

Recommendations

- **Early** and proactive discussions with the appropriate review division on how best to plan for the interpretation of study findings to avoid conducting studies that are not able to support your desired labeling/promotional claims
  - Review divisions will consult with the COA Staff and/or OPDP as necessary.
  - Target Product Profile

Conclusions

- **Labeling has a significant impact on drug promotion.**
- **Early communications with FDA is the key to optimizing your goals!**

OPDP Contact Information

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5901-B Ammendale Road
Beltsville, MD 20705-1266

OPDP Web Resources

- **OPDP home page**

  http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm

- **OPDP organization listing**

  http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm154886.htm

- **Guidances**

  http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm109905.htm#Guidances

- **Warning and untitled letters**

  www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/default.htm