



Santosh T. Varghese, M.D.
Chief Medical Officer
VIVUS, Inc.
900 East Hamilton Avenue, Suite 550
Campbell, CA 95008

RE: NDA 022580

QSYMIA (phentermine and topiramate extended-release) capsules, for oral use, CIV
MA 414

Dear Dr. Varghese,

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the homepage of the consumer website¹ (webpage) [100028.42-USP] for QSYMIA (phentermine and topiramate extended-release) capsules, for oral use, CIV (Qsymia) submitted by VIVUS, Inc. (Vivus) under cover of Form FDA 2253. The webpage makes false or misleading claims and/or representations about the efficacy of and risks associated with Qsymia. As a result, the webpage misbrands Qsymia within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), and makes distribution of the product violative. 21 U.S.C. 352(a),(n); 331(a); 321(n). See 21 CFR 202.1(e)(1); 202.1(e)(5); 202.1(e)(7)(viii). The webpage is especially concerning from a public health perspective because it creates a misleading impression regarding the overall effect a patient may expect as a result of Qsymia treatment and deemphasizes the risks associated with taking the drug. Obesity and excessive weight are significant public health concerns that affect millions of adults in the United States and are associated with numerous co-morbidities. Consumers and patients who seek assistance with their weight-loss goals should not be misled regarding the actual benefits, serious risks, and necessary nutritional and lifestyle modifications associated with the use of a weight management prescription drug product, such as Qsymia.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Qsymia.² According to the FDA-approved product labeling (PI) (emphasis original):

Qsymia is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of

¹ Found at <https://qsymia.com> (last accessed May 22, 2019).

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

- 30 kg/m² or greater (obese), or
- 27 kg/m² or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia

Limitations of Use

- The effect of Qsymia on cardiovascular morbidity and mortality has not been established.
- The safety and effectiveness of Qsymia in combination with other products intended for weight loss, including prescription and over-the-counter drugs and herbal preparations have not been established.

This product is associated with a number of serious risks. Qsymia is contraindicated in pregnancy, glaucoma, hyperthyroidism, during or within 14 days following the administration of monoamine oxidase inhibitors, and in patients with a known hypersensitivity or idiosyncrasy to the sympathomimetic amines. The PI for Qsymia contains warnings and precautions regarding fetal toxicity, increases in heart rate, suicidal behavior and ideation, acute myopia and secondary angle closure glaucoma, mood and sleep disorders, cognitive impairment, metabolic acidosis, elevation in creatinine, potential risk of hypoglycemia in patients with type 2 diabetes mellitus on anti-diabetic therapy, potential risk of hypotension in patients treated with antihypertensive medications, CNS depression with concomitant CNS depressants including alcohol, potential seizures with abrupt withdrawal of Qsymia, patients with renal impairment, patients with hepatic impairment, kidney stones, oligohidrosis and hyperthermia, hypokalemia, and monitoring laboratory tests. The most common adverse reactions associated with Qsymia are paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth.

False or Misleading Claims about Efficacy

Promotional materials misbrand a drug if they are false or misleading with respect to efficacy. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure 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 materials.

The webpage includes the following claims (bolded emphasis original, underlined emphasis added):

- **“On average, prescription Qsymia can help you lose weight 3 times faster than diet and exercise alone.^[3,4]”**
- **“3X FASTER WEIGHT LOSS”**

These claims misleadingly suggest that Qsymia can help patients lose weight 3 times faster than diet and exercise alone. However, the cited references^{3,4} do not support this suggestion

³ Qsymia Full Prescribing Information. Campbell, CA: VIVUS, Inc; 2018

⁴ Data on File. VIVUS. Inc.

and we are not aware of data to support these claims. First, the Data on File⁴, which is cited on the webpage as support, reports calculated ratios of the average absolute amount of weight loss for Qsymia compared to placebo at week 12, 28, and 56. However, the cited calculations do not support the rate of weight loss since they describe the amount of weight loss at specific points in time. Additionally, although the calculations were derived from the clinical studies included in the PI, they cannot support a claim of “faster” weight loss because the studies were not designed to evaluate the rate of weight loss over time. According to the CLINICAL STUDIES section of the PI, the co-primary efficacy outcomes measured the amount of weight loss after 1 year of treatment (a fixed point in time) as the percent of weight loss from baseline weight and treatment response (defined as achieving at least 5% weight loss from baseline). These studies were designed to evaluate the amount of weight loss and cannot be used to support claims regarding rate of weight loss. Therefore, the cited references do not support the misleading suggestion that Qsymia can help patients lose weight 3 times faster than diet and exercise alone. If you have data to support these claims, please submit such data to FDA for review.

The webpage also presents the following claims (emphasis original):

- “For patients with a body mass index (BMI)* of 30+[†] or 27 kg/mg² or greater (overweight) in the presence of at least one weight-related medical condition.

Lose weight and keep it off with Qsymia^[3,4]

. . . .

12 Weeks

Your first milestone

15-19 Pounds of weight loss 2-3 Inches off your waist

28 Weeks

Stay motivated

22-29 Pounds of weight loss 3-4 Inches off your waist

56 Weeks

Maintain progress

24-32 Pounds of weight loss 4-5 Inches off your waist”

This presentation omits material information from the full indication about the relative effect of diet and exercise. According to the INDICATIONS AND USAGE section of the PI, Qsymia is indicated as an adjunct to a reduced-calorie diet and increased physical activity. This presentation is misleading because it does not include this important information. We note that the webpage contains illustrations showing an exercise bike, a bag of groceries, and a capsule. However, these are not adequate to convey to the viewer that both exercise and diet are necessary in achieving the benefits (weight management) of Qsymia as stated in the PI. Additionally, the omission of contextual information about the results observed in the placebo group creates a misleading presentation because it suggests that these results are or can be attributable to Qsymia alone.

In addition, this presentation creates a misleading impression regarding the efficacy of Qsymia by selectively presenting more favorable data. Specifically, this presentation selectively presents the more favorable absolute amount of weight loss and reduction in waist circumference, which fails to account for an individual's baseline weight and waist circumference. According to the CLINICAL STUDIES section of the PI, these efficacy outcomes were measured in the context of a patient's baseline weight and waist circumference. By failing to account for an individual's baseline weight and waist circumference and omitting this context on the webpage, this presentation misleadingly implies that all patients, no matter their baseline weight or waist circumference, should expect to achieve results similar to the absolute amounts presented on the webpage under the claims "Your first milestone," "Stay motivated" and "Maintain progress."

Finally, this presentation primarily reflects patient data⁵ from distinct points during the clinical trials of only those who remained on Qsymia. According to the CLINICAL STUDIES section of the PI, a substantial percentage of patients withdrew their participation from the studies prior to the conclusion of the trials at week 56 - 40% in Study 1 and 31% in Study 2. The above claims fail to account for these patients who withdrew from the studies. By selectively presenting results without this contextual information, the presentation overstates the efficacy of the product and misleadingly implies all patients who received Qsymia remained on treatment.

False or Misleading Risk Presentation

Promotional materials misbrand a drug if they are false or misleading with respect to risk. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure 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 materials.

The webpage fails to present information relating to contraindications, warnings, precautions, and adverse reactions for Qsymia with a prominence and readability reasonably comparable with the presentation of information relating to the benefits of Qsymia. Factors impacting prominence and readability include typography, layout, contrast, headlines, paragraphing, white space, and other techniques apt to achieve emphasis. Specifically, benefit claims for Qsymia are presented in conjunction with colorful graphics and large bolded headlines, with significant white space. However, the risk information is relegated to the bottom of the webpage in paragraph format and is not easily accessible to viewers who must "scroll" down the webpage past the entire benefit presentation. Additionally, the webpage does not present any significant signal to alert the viewer that important risk information follows the presentation of benefit information.

Conclusion and Requested Action

For the reasons discussed above, the webpage misbrands Qsymia within the meaning of the FD&C Act and makes distribution of the product violative. 21 U.S.C. 352(a),(n); 331(a); 321(n). See 21 CFR 202.1(e)(1); 202.1(e)(5); 202.1(e)(7)(viii).

⁵ The data is primarily derived from three subset populations who remained on treatment at Weeks 12, 28, and 56, respectively.

OPDP requests that Vivus immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before June 7, 2019, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Vivus that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

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 Amundson Avenue, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 414 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. OPDP reminds you that only written communications are considered official.

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

Sincerely,

{See appended electronic signature page}

Meena Savani, PharmD, RAC
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

{See appended electronic signature page}

Melinda McLawhorn, PharmD, MPH, BCPS,
RAC
Team Leader
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MEENA R SAVANI
05/22/2019 08:21:44 PM

MELINDA W MCLAWHORN
05/22/2019 08:26:56 PM