DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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DEC 14 2012

Joseph Dedvukaj
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Re: Docket No. FDA-2012-P-0764

Dear Mr. Dedvukaj:

This letter responds to your citizen petition received on July 17, 2012 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or Agency) decline to approve Vivus Inc.'s (Vivus) new drug application (NDA) for QNEXA (NDA 22-580).[1] FDA has carefully considered the information submitted in your petition and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, your petition is denied.

I. BACKGROUND

A. QSYMIA

QSYMIA is a fixed-dose combination of immediate-release phentermine hydrochloride (phentermine) and extended-release topiramate (topiramate ER). Vivus's NDA, submitted on December 28, 2009, sought approval of QSYMIA for the treatment of adult obesity, including weight loss and maintenance of weight loss when used in conjunction with diet and exercise. The proposed indication included obese patients (body mass index [BMI] $\geq$ 30 kilograms (kg)/square meter (m^2) or overweight patients (BMI $\geq$ 27 kg/m^2) with obesity-related comorbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

The NDA was the subject of a July 15, 2010, Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting. The EMDAC voted against approval of QSYMIA at that meeting. On October 28, 2010, FDA's Division of Metabolism and Endocrinology Products (DMEP) issued a Complete Response Letter (CRL) to Vivus, citing as deficiencies the application's insufficient assessment of QSYMIA's cardiovascular risk and teratogenic potential.[2] Vivus submitted its response to the CRL on October 17, 2011, which included a

[1] NDA 22-580 was originally submitted with the proposed trade name "QNEXA." Vivus subsequently changed the proposed trade name to QSYMIA. For clarity, we will refer to the drug product as QSYMIA in this response.
[2] See clinical briefing document, Endocrinologic and Metabolic Drugs Advisory Committee Meeting, February 22, 2012, NDA 22580: VI-0521 QNEXA (phentermine/topiramate) (AC Clinical Briefing Document), at 1-2, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM292315.pdf.

cardiovascular risk analysis report for QSYMIA and a review of topiramate's and QSYMIA's teratogenic potential.[3] In February of 2012, EMDAC members met again to review the data submitted by Vivus in their response to the CRL. At that meeting, the EMDAC voted 20 to 2 in favor of QSYMIA approval.[4]

FDA approved the NDA for QSYMIA on July 17, 2012.[5] In doing so, FDA determined that a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use was necessary to ensure that the benefits of QSYMIA outweigh the risks of congenital malformations (specifically orofacial clefts) in infants exposed to QSYMIA during the first trimester of pregnancy.[6] The goal of the QSYMIA REMS, which includes a medication guide, a prescriber training program, a pharmacy certification program, and an implementation system, is to inform prescribers and female patients of reproductive potential about (1) the increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to QSYMIA during the first trimester of pregnancy, (2) the importance of pregnancy prevention for females of reproductive potential receiving QSYMIA, and (3) the need to discontinue QSYMIA immediately if pregnancy occurs.[7]

B. Phentermine and Topiramate

Both phentermine and topiramate are approved individually for other indications and are available at higher doses than are present in QSYMIA.[8] Phentermine was approved in 1959 as an appetite suppressant. Since 1973, it has been indicated for short-term use only.[9] Phentermine is approved in doses up to 37.5 milligrams (mg)/day.[10] The approved labeling for phentermine lists adverse cardiovascular events that are associated with its use and states that use is contraindicated in patients with a history of cardiovascular disease.

Topiramate was approved in 1996 for the treatment of seizures and in 2004 for the prevention of migraine headache. The approved doses for topiramate are up to 400 mg/day for seizures and up to 100 mg/day for migraine prophylaxis.[11] Topiramate's labeling specifies that it is a Pregnancy Category D[12] drug, and can cause fetal harm when administered to pregnant women (including

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[3] Id.

[4] See Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting – February 22, 2012, at 7, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM304401.pdf.

[5] Approval Letter, NDA 22-580 (Approval Letter), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022580Origs000ltr.pdf.

[6] See Approval Letter at 7-11.

[7] Id.

[8] QSYMIA is available in the following doses: 3.75 mg phentermine/23 mg topiramate ER; 7.5 mg phentermine/46 mg topiramate ER; 11.25 mg phentermine/69 mg topiramate ER; and 15 mg phentermine/92 mg topiramate ER.

[9] The phentermine labeling defines 'short term' as a few weeks.

[10] See AC Clinical Briefing Document at 1.

[11] Id.

[12] "Pregnancy Category D" means that there is positive evidence of human fetal risk from use of the drug based on human data, but that the potential benefits from use of the drug in pregnant women may be acceptable in certain situations despite its risks. See 21 CFR 201.57(c)(9)(i)(A)(4).

an increased risk of oral clefts in infants exposed in utero). The risk of oral clefts resulting from in utero exposure to topiramate was also the subject of a March 4, 2011, FDA Drug Safety Communication.[13]

C. Petition

Your petition requests that FDA decline to approve Vivus's NDA for QSYMIA. You argue that there has been insufficient assessment of teratogenicity associated with QSYMIA, and that final results from the Fetal Outcomes Retrospective Topiramate Exposure Study (FORTRESS) are necessary to determine whether QSYMIA is safe (Petition at 1-3). You state that the cardiovascular risks of QSYMIA in obese patients with cardiovascular comorbidities have also been inadequately assessed (Petition at 5). You assert that a REMS for QSYMIA would likely be impractical, burdensome, and ineffective because topiramate and phentermine are individually available without a REMS (Petition at 3-5, 8-9). Finally, you urge FDA not to approve QSYMIA until it has developed mechanisms to actively discourage off-label combination use of phentermine and topiramate drug products (Petition at 3-4).

D. Legal Framework

1. 505(b)(2) Applications

Under the Federal Food, Drug and Cosmetic Act (FD&C Act), sponsors seeking to market a new drug generally must first submit an application to FDA for approval. An NDA contains, among other things, extensive scientific and clinical data demonstrating the safety and effectiveness of the drug (see sections 505(a) and (b) of the FD&C Act, 21 U.S.C. 355(a) and (b)). Under section 505(b)(2) of the FD&C Act, a sponsor may submit an application for approval that relies, at least in part, on investigations that were not conducted by or for the applicant and to which the applicant does not have a right of reference. A 505(b)(2) application, like any NDA, must contain information adequate to show that the drug is safe and effective and must include data necessary to support the safety and effectiveness of any aspects of the proposed drug product that represent modifications to or changes from the listed drug on which it relies. The QSYMIA application, which relies in part on FDA's previous determinations of safety for phentermine and topiramate, was submitted pursuant to section 505(b)(2) of the FD&C Act.[14]

2. Petitions Subject to Section 505(q) of the FD&C Act

Under section 505(q)(1)(A)(ii) of the FD&C Act, FDA may not delay the approval of a pending 505(b)(2) or (j) application based on a request to take any form of action relating to the application, either before or during consideration of the request, unless (among other things) the

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[13] FDA Drug Safety Communication: Risk of oral clefts in children born to mothers taking TOPAMAX (topiramate), *available at:* http://www.fda.gov/Drugs/DrugSafety/ucm245085.htm.

[14] See Vivus, Inc., VI-0521 (QNEXA) Advisory Committee Briefing Document, NDA 22-580, Endocrinologic and Metabolic Drugs Advisory Committee Meeting (February 22, 2012), at 2, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM292317.pdf.

Agency determines, "upon reviewing the petition, that a delay is necessary to protect the public health."[15] Because your petition requests action that could have delayed approval of a then-pending 505(b)(2) application, the Petition is subject to the requirements of section 505(q) of the FD&C Act.[16] FDA guidance on 505(q) petitions states that, unless a petition may be summarily denied because FDA concludes that its primary purpose is to delay approval and it does not, on its face, raise valid scientific or regulatory issues, FDA is to determine whether the application would be ready for approval but for the petition, and if so, whether a delay is necessary to protect the public health based on its preliminary evaluation of the issues raised in the petition.[17] Prior to approving NDA 22-580, FDA completed this evaluation and determined, for the reasons described in this response, that a delay of approval was not necessary to protect the public health.[18]

3. Approval of Drug Products with REMS

Section 505-1(a)(1) of the FD&C Act (21 U.S.C. 355-1(a)(1)) authorizes FDA to require applicants[19] to submit a proposed REMS when FDA has determined that a REMS is necessary to ensure that the benefits of a drug outweigh its risks.[20] A REMS is a required risk management plan that uses tools beyond routine professional labeling (such as medication guides, patient package inserts, and/or communication plans) to ensure that the benefits of a drug outweigh its risks. In addition, FDA may require certain "elements to assure safe use" (ETASU) when additional elements are necessary to mitigate the risks associated with a drug.[21] ETASU may include, for example, requirements that healthcare providers who prescribe the drug have particular training or experience or are specially certified, that patients using the drug be monitored and/or enrolled in a registry, or that pharmacies, practitioners, or health care settings that dispense the drug be specially certified.[22]

The decision that a REMS is necessary to ensure that the benefits outweigh the risks of a particular drug is a fact-specific inquiry that requires consideration of the following factors: (1)

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[15] We note that your petition (FDA-2012-P-0738) was initially received on July 11, 2012 – less than one week prior to the PDUFA goal date for QSYMIA – but it lacked the complete certification required under section 505(q)(1)(H) of the FD&C Act. FDA contacted you on July 12, 2012 to highlight this deficiency (as well as the Petition's lack of an Environmental Impact Statement) and to notify you that unless the certification deficiency was cured, the Petition would be unreviewable under the statute. You withdrew the original petition and resubmitted it with the proper certification on July 17, 2012. The resubmitted petition was assigned docket number FDA-2012-P-0764.

[16] Guidance for industry on *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug and Cosmetic Act* (June 2011) at 4-5.

[17] Id. at 7-8.

[18] See Memo from Dr. Eric Colman, Deputy Director, DMEP, to file, NDA 22580 – Vivus Pharmaceuticals Qsymia (fixed-dose combination of phentermine and extended-release topiramate) capsules - 3.75/23 mg; 7.5/46 mg; 11.25/69 mg; and 15/92 mg re: Citizen Petition Seeking to Delay Approval of Vivus' NDA 22580 (Colman Memo).

[19] Section 505-1 of the FD&C Act applies to any application for approval of a prescription drug submitted under sections 505(b) or (j) of the FD&C Act (thus including both NDAs submitted under section 505(b)(2) and ANDAs submitted under 505(j)), as well as applications submitted under section 351 of the Public Health Service Act.

[20] 21 U.S.C. 355-1(a)(1).

[21] 21 U.S.C. 355-1(f)(3).

[22] Id.

the estimated size of the population likely to use the drug, (2) the seriousness of the disease or condition to be treated, (3) the expected benefit of the drug with respect to the disease or condition, (4) the expected or actual duration of treatment with the drug, (5) the seriousness of known/potential adverse events that may be related to the drug and the background incidence of these events in the population likely to use the drug, and (6) whether the drug is a new molecular entity.[23]

II. DISCUSSION

A. Teratogenicity

As described above, your petition argues that the assessment of QSYMIA's teratogenicity was insufficient, and that final results from the FORTRESS Study are necessary to adequately assess teratogenicity associated with the topiramate component of QSYMIA (Petition at 2-3).

FDA considered the following teratogenicity data in reviewing the NDA for QSYMIA: the North American Antiepileptic Drug Pregnancy Registry; the Australian Pregnancy Register; the United Kingdom Pregnancy and Epilepsy Register; and the Israeli Teratogen Information Service; FDA's Adverse Event Reporting System; an observational study conducted by the Centers for Disease Control and Prevention (CDC) and the Slone Epidemiology Center at Boston University; interim data from the FORTRESS study; and an observational study published by Wolters Kluwer.[24]

Based on these data, FDA concluded that: (1) there is no evidence of an increased risk of overall major congenital malformations with topiramate exposure; (2) first trimester topiramate exposure is associated with an increased risk of oral clefts; and (3) the estimated relative risks of oral clefts were unstable, but could range from twofold up to fivefold based on the currently available point estimates.[25] Given that the data suggest that topiramate, at the doses present in QSYMIA, increases the risk of oral clefts and that the expected patient population likely would include women of childbearing potential, FDA determined that a REMS was necessary to ensure that the benefits of QSYMIA outweigh the potential teratogenic risk.[26] FDA specifically considered whether it was necessary to wait for final FORTRESS study data, and concluded that the body of evidence before the Agency at the time of approval was sufficient to make an assessment of QSYMIA's teratogenic risk and how it affects QSYMIA's benefit-risk profile.[27]

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[23] 21 U.S.C. 355-1(a).

[24] Margulis AV, Mitchell AA, Gilboa SM, et al., 2012, Use of topiramate in pregnancy and risk of oral clefts. Am J Obstet Gynecol 2012;207:1.e1-7; Green MW, Seeger JD, Peterson C, and Bhattacharyya A, 2012, Utilization of Topiramate During Pregnancy and Risk of Birth Defects. Headache. 2012 Jul-Aug;52(7):1070-84; Clinical Review: Complete Response Submission, Dr. Mary Dunne Roberts (Roberts Review), Section 7.6.2 (July 17, 2012).

[25] See Deputy Division Director Summary Review, Dr. Eric Colman (Colman Review), Section 7 -- Teratogenicity, at 8 (July 17, 2012).

[26] Id.

[27] See Roberts Review, Section 7.6.2; Deputy Division Director Summary Review, Dr. Eric Colman, Section 7 -- Teratogenicity (July 17, 2012); Colman Memo at 2.

B. Cardiovascular Risks

Your petition also notes that QSYMIA is associated with an increase in resting heart rate and argues that there has not been adequate characterization of QSYMIA's increase in heart rate in higher risk cardiovascular populations (Petition at 5). You further maintain that without studying greater numbers of higher risk patients, "it is unclear how the label could adequately guide prescribers to use [QSYMIA] in a safe manner."[28]

FDA's analysis of the data regarding QSYMIA's effect on heart rate and cardiovascular risk is described in detail in the reviews of Vivus's complete response submission.[29] As discussed there, although QSYMIA is associated with a small mean increase in heart rate, it reduces blood pressure to a greater extent than it increases heart rate. The change in the rate-pressure product (heart rate x systolic blood pressure) – a surrogate of myocardial oxygen demand – is similar for QSYMIA and placebo-treated subjects.[30] In addition, analyses of cardiovascular-related adverse event data from the QSYMIA phase 2 and 3 clinical trials, while limited in scope, do not raise concerns of excessive risk.[31]

The clinical review of Vivus's complete response submission acknowledges that the labeling should inform healthcare providers and patients of the evidence, the limitations, and ways to mitigate cardiovascular risk.[32] Accordingly, QSYMIA's labeling recommends that prescribers monitor heart rate in all patients, especially those with cardiac or cerebrovascular disease.[33] The labeling also states that QSYMIA has not been studied in patients with advanced or unstable cardiovascular and cerebrovascular disease, and therefore its use is not recommended in those patients.[34] Finally, the sponsor is required, post-approval, to conduct a randomized, double-blind, placebo-controlled trial to prospectively evaluate the long-term effect of QSYMIA on the incidence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors.[35]

C. Risk Evaluation and Mitigation Strategy

You also argue that there is insufficient information to show that the proposed REMS for QSYMIA will adequately protect against fetal exposure to topiramate, a teratogen (Petition at 1). You contend that a REMS is unlikely to be effective, because topiramate and phentermine drug products are available separately without a REMS, and suggest that approval of QSYMIA with a REMS will encourage off-label combination use of the individual drug products for weight loss

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[28] Id.
[29] See Roberts Review, Section 7.3.5; Coleman Review, Section 7 – Heart Rate and Blood Pressure.
[30] See Roberts Review, Section 7.3.5 at 150-152; Coleman Review, Section 7 – Heart Rate and Blood Pressure & Section 12 -- Decision/Action/Risk Benefit Assessment.
[31] Colman Memo at 3.
[32] Roberts Review, Section 7.3.5, at 167.
[33] See QSYMIA labeling (approved July 17, 2012) WARNINGS AND PRECAUTIONS section 5.2, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022580s000lbl.pdf.
[34] Id.
[35] See Approval Letter at 7.

(Petition at 3-5, 8-9). You argue that until effective mechanisms are identified that would actively discourage such off-label use, we should not approve QSYMIA (Petition at 3-4). As described above, a REMS applies to a specific drug product, and is required under section 505-1(a) of the FD&C Act when FDA determines that a REMS is necessary for the benefits of a drug to outweigh the risks. The REMS for QSYMIA was developed on the basis of an analysis of the six factors set forth in section 505-1(a) of the FD&C Act. Whether the individual components of QSYMIA are available without a REMS does not affect whether the QSYMIA REMS is effective in mitigating the risk of oral clefts in infants exposed to QSYMIA during the first trimester of pregnancy.

Nevertheless, in crafting the REMS, FDA did consider the potential for off-label prescribing of the component drugs for weight loss.[36] As a result, the REMS was designed to inform patients and health care providers about the teratogenic risks associated with QSYMIA and to limit dispensing to specially certified pharmacies, while not introducing unnecessary burdens on the use and prescribing of QSYMIA that might indirectly serve to encourage off-label combination use of phentermine and topiramate drug products.[37]

Further, the Agency has tools at its disposal to ensure that the REMS for QSYMIA is meeting its goals and mitigating the risk of teratogenicity posed by QSYMIA. The REMS requires that assessments be submitted to FDA at 6 months and 12 months after approval, and annually thereafter.[38] If, upon review of the required assessments (or for any reason), FDA determines that changes to the REMS are necessary to ensure that the benefits of the drug outweigh the risks, it can require modification of the REMS.[39]

To the extent that you are suggesting that approval of QSYMIA will affect the safety profile of topiramate, a separate drug product, delaying approval of QSYMIA would not have been the appropriate remedy. Should the safety profile of topiramate change for any reason, FDA can address related safety concerns using its range of tools and authorities under the FD&C Act, including requiring safety labeling changes under section 505(o) of the FD&C Act or withdrawing approval under section 505(e). Moreover, to the extent that healthcare providers likely to prescribe topiramate and phentermine drug products in combination for weight loss are part of the target group for training and education under the QSYMIA REMS – which includes health care providers who have written a prescription for a weight loss treatment within the last 12 months – they will be provided information under the REMS regarding the teratogenic risks.[40]

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[36] See, e.g., FDA Presentations for the February 22, 2012, Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee, Joyce Weaver, Senior Drug Risk Management Analyst, FDA: "Risk Management Options for Phentermine/Topiramate" at 11, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM293905.pdf.

[37] See 21 U.S.C. 355-1(f)(2)(C).

[38] QSYMIA REMS at 5, available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM312598.pdf.

[39] 21 U.S.C. 355-1(g)(4)(B).

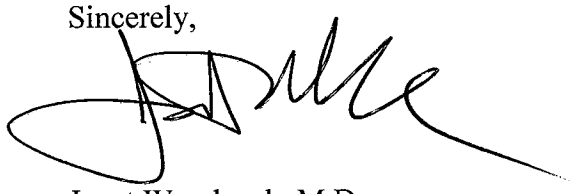
[40] Id.

Finally, the sponsor will be required to conduct a prospective cohort study to determine the frequency of pregnancy in QSYMIA patients and to compare the risk of oral clefts and major congenital malformations in the offspring of women exposed to QSYMIA during pregnancy with women who were not so exposed. The sponsor also will be required to conduct an annual drug use study for seven years to assess adverse event reporting rates of orofacial clefts in infants exposed to QSYMIA during the first trimester of pregnancy and to assess possible risk factors contributing to the risk. The Agency will carefully monitor this information and any other safety reports and usage patterns, and take additional regulatory actions as appropriate.

III. CONCLUSION

As discussed in detail in the medical reviews accompanying QSYMIA approval, FDA concluded that the benefits of QSYMIA outweigh its risks, and that it should be approved. FDA believes that the REMS designed for QSYMIA will adequately mitigate the teratogenic risks associated with its use for chronic weight management. The arguments raised by the Petition do not change these conclusions. For the reasons described above, the Petition is denied.

Sincerely,



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