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APPLICATION NUMBER:
22580Orig1s000

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022580

NDA APPROVAL

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) dated December 28, 2009, received December 28, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Qsymia (phentermine and topiramate extended-release) Capsules CIV.

We acknowledge receipt of your amendments dated January 18 (2), February 5, March 2, 5, 12, 18, 24, 31 (2), April 11, 20 (2), 23, 26, 29, May 6, 11, 12, 14, 15, 16, 27, June 16 (2), 23, 29, 30, July 1, 8 (4), 27, August 6 (2), 18 (2), 26 (2), September 14, October 5, November 10, December 12, 2010, January 6, February 3, March 4, 18, April 21, May 27, June 15, September 14, 21, October 12, 14, 21, November 16, 18, 22, December 2, 19, 21, 22, 28, 2011, January 11 (2), 12, 13, 17, 19, 24, 27, February 2 (3), 20, 28, March 9, March 26, 29, 29, April 3, 4, 9, 11 (2), 16, 17, 18 (2), 24, May 9, 25, 31, June 5 (2), 11, 21, 29 (3), July 5, 9, and July 17, 2012.

The October 14, 2011, submission constituted a complete response to our October 28, 2010, action letter.

This new drug application provides for the use of Qsymia (phentermine and topiramate extended-release) capsules CIV as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of 30 kg/m² or greater (obese) or 27 kg/m² or greater (overweight) when accompanied by weight-related co-morbidities such as hypertension, type 2 diabetes mellitus, or dyslipidemia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your July 17, 2012, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 6 years (inclusive) because there is evidence strongly suggesting that the drug product would be ineffective and unsafe in this pediatric group. Current recommendations favor weight maintenance for the majority of affected children in this age group through modifications of diet and exercise. Treatment with topiramate, a component of Qsymia (phentermine and topiramate extended-release), in children in this age group for other indications has been associated with metabolic acidosis, oligo- or hypohydrosis, and hyperthermia at rates which may be higher than those observed in adults. If present, such effects would represent a greater safety concern in children than in adults. There is limited data on the efficacy and safety of phentermine, a component of Qsymia, in this age group. Both phentermine and topiramate are centrally acting drugs which may have significant effects on normal growth and development, learning, memory, and behavior.

We are deferring submission of your pediatric studies for ages 7 to 17 years (inclusive) for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected. Pediatric trials in the adolescent age group (12 to 17 years) should be delayed until further data from juvenile animal models on bone health and neurocognitive

function are assessed. Pediatric trials in the pre-adolescent age group (7 to 11 years) should be delayed until the results of the Qsymia adolescent safety and efficacy study have been submitted and reviewed by the Agency.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1901-1 A clinical pharmacology trial to assess pharmacokinetic and pharmacodynamic parameters related to Qsymia doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg in pediatric patients ages 12 to 17 years (inclusive). Data from this trial should be considered when choosing dose(s) for the safety and efficacy trial in this pediatric population. This trial should not be initiated until after the data from the juvenile animal study have been submitted and reviewed by the Agency.

Final Protocol Submission: June 2015
Trial Completion: November 2015
Final Report Submission: May 2016

1901-2 A 52-week randomized, double-blind, placebo-controlled pediatric trial to evaluate the safety and efficacy of Qsymia for the treatment of obesity in pediatric patients ages 12 to 17 years (inclusive). This trial should not be initiated until after the data from the juvenile animal study have been submitted and reviewed by the Agency.

Final Protocol Submission: November 2016
Trial Completion: March 2018
Final Report Submission: September 2018

1901-3 A clinical pharmacology trial to assess pharmacokinetic and pharmacodynamic parameters related to Qsymia doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg in pediatric patients ages 7 to 11 years (inclusive). Data from this trial should be considered when choosing dose(s) for the safety and efficacy trial in this pediatric population. You may not initiate this trial until the results of the Qsymia adolescent safety and efficacy trial have been submitted to and reviewed by the Agency.

Final Protocol Submission: March 2019
Trial Completion: June 2019
Final Report Submission: December 2019

1901-4 A 52-week randomized, double-blind, placebo-controlled pediatric trial to evaluate the safety and efficacy of Qsymia for the treatment of obesity in pediatric patients ages 7 to 11 years (inclusive). You may not initiate this trial until results

from the Qsymia adolescent safety and efficacy trial have been submitted to and reviewed by the Agency.

Final Protocol Submission: June 2019
Trial Completion: October 2021
Final Report Submission: April 2022

Submit the clinical protocols to your IND 068651, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- Assess a known serious risk of congenital malformation (specifically orofacial clefts) in infants exposed to Qsymia (phentermine and topiramate extended-release) during the first trimester of pregnancy;
- Assess signals of serious risks of adverse effects on bone health with exposure to Qsymia (phentermine and topiramate extended-release), or potential harm to bone, teeth, and nervous system development if children and adolescents are exposed to Qsymia (phentermine and topiramate extended-release);
- Identify unexpected serious risks of ocular toxicity and impairment in behavior, learning and memory if children and adolescents are exposed to Qsymia (phentermine and topiramate extended-release).
- Assess a signal of a serious risk of dose-related increases in serum creatinin possibly due to a potential for inhibiting renal transport proteins.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1901-5 A juvenile animal study with phentermine and topiramate extended-release co-administration to assess effects on behavior, learning and memory; ocular toxicity; and effects on general nervous system and bone/teeth development. The

study should include assessments of drug exposure and reversibility of any observed toxicity.

The timetable you submitted on June 21, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: April 2013
Study Completion: February 2014
Final Report Submission: December 2014

- 1901-6 An *in vitro* study to determine the inhibition potential of both phentermine and topiramate extended-release individually and in combination on the following human transporters: organic cation transporter2 (OCT2) and OCT3; organic anion transporter3 (OAT3) and OAT4; multidrug and toxin extrusion protein1 (MATE1) and MATE2-K.

The timetable you submitted on June 21, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: September 2012
Study Completion: March 2013
Final Report Submission: September 2013

- 1901-7 A prospective cohort study to a) determine the frequency of pregnancy in women of child-bearing age prescribed Qsymia and b) compare the risk of oral clefts, major congenital malformations, and low birth weight in offspring of women exposed to Qsymia during pregnancy with offspring of similar women not exposed to Qsymia during pregnancy.

The timetable you submitted on June 21, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: October 2012
Interim Report Submissions: July 2014
July 2015
July 2016
July 2017
July 2018
Study Completion: July 2019
Final Report Submission: October 2019

- 1901-8 A drug-use study conducted annually for 7 years with nationally representative and projected data to provide a denominator in order to assess adverse event reporting rates of the known serious risk of congenital malformation (specifically orofacial clefts) in infants exposed to Qsymia during the first trimester of pregnancy, and to assess possible risk factors contributing to the risk. Provide the

following about patients prescribed Qsymia: a) the estimated total number of prescriptions and patients dispensed Qsymia per year; b) distribution of patients by age, sex, and BMI; c) distribution of prescribers by specialty; d) average, median, and range for duration of use; e) average and median size of prescriptions; f) prescribed average daily dose; g) frequencies of top 10 concomitant diagnoses (including pregnancy) by age and sex; h) frequencies of top 10 concomitant drugs by age and sex (including contraceptive medications for females of childbearing age).

The timetable you submitted on June 21, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 2012
Interim Report Submissions:	July 2013
	July 2014
	July 2015
	July 2016
	July 2017
	July 2018
Study Completion:	September 2019
Final Report Submission:	December 2019

Finally, there have been signals of a serious risk of major adverse cardiovascular events with some medications developed for the treatment of obesity, and available data have not definitively excluded the potential for this serious risk with Qsymia (phentermine and topiramate extended-release). We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with anti-obesity medications, including Qsymia (phentermine and topiramate extended-release). We have also determined that only a clinical trial will be sufficient to assess a signal of serious risks of possible decreases in glomerular filtration rate (GFR) associated with the use of Qsymia (phentermine and topiramate extended-release), and adverse effects on bone health in adults with Qsymia (phentermine and topiramate extended-release).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1901-9 A randomized, placebo- and active-controlled trial to evaluate changes in renal function in obese adults, who will be randomized to Qsymia (3 dosage strengths) or placebo. The primary objective of the trial will be to assess the change in measured GFR (assessed as urinary clearance of 125I-sodium iothalamate). Depending on the results of short-term Qsymia exposure on measured GFR, longer follow-up of affected individuals may be required.

The timetable you submitted on June 21, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: September 2012
Trial Completion: June 2013
Final Report Submission: December 2013

- 1901-10 A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with Qsymia on the incidence of major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors. A subset of individuals should have measurements of bone health assessed by serial radiographic and laboratory measurements. Measurements of autonomic function (heart rate variability, baroreceptor sensitivity) and dynamic testing (24-hour blood pressure and heart rate monitoring) should also be assessed in a subset of individuals.

The timetable you submitted on June 21, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: July 2012
Trial Completion: June 2017
Final Report Submission: December 2018

Submit the protocols to your IND 068651, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our complete response letter dated October 28, 2010. Subsequent to this letter, and following discussion at a February 22, 2012 Advisory Committee meeting, it was determined that your REMS should include elements to assure safe use.

Pursuant to 505-1(f)(1), we determined that Qsymia (phentermine and topiramate extended-release) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of congenital malformation (specifically orofacial clefts) in infants exposed to Qsymia during the first trimester of pregnancy. The elements to assure safe use will inform prescribers and females of reproductive potential about this risk, and the importance of pregnancy prevention and the need to discontinue Qsymia immediately if a pregnancy occurs. The elements to assure safe use will also limit dispensing of Qsymia to only certified pharmacies that agree to distribute the Qsymia Medication Guide and the *Risk of Birth Defects with Qsymia* patient brochure each time Qsymia is dispensed and to maintain a list of Qsymia prescribers.

At this time, your proposed REMS that includes dispensing through mail-order pharmacies is ready for approval. However, we request that you submit a REMS modification that will facilitate dispensing through a broader range of pharmacies as soon as you have developed an acceptable plan for doing so.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on July 17, 2012, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Qsymia (phentermine and topiramate extended-release) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. Results of an evaluation of patients' understanding of the serious risks of Qsymia (phentermine and topiramate extended-release).
2. Using data obtained from surveys of patients and prescribers, an evaluation of the extent that females of reproductive potential were counseled about pregnancy prevention and contraceptive use.
3. Using data obtained from surveys of patients, an evaluation of contraceptive use by females of reproductive potential.

4. An assessment of healthcare providers' awareness of:
 - a. The serious risks of Qsymia (phentermine and topiramate extended-release)
 - b. The need to exclude a pregnancy before initiating Qsymia therapy
 - c. The need for patients to consistently use effective birth control and what the effective methods of contraception are
 - d. The need to promptly discontinue Qsymia therapy in the event of a pregnancy.
5. A report on pharmacy failures to adhere to distribution and dispensing requirements based on audits conducted by Vivus.
6. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24, and patient brochure entitled *Risk of Birth Defects with Qsymia*.
7. A report on failures to adhere to dispensing requirements based on pharmacy self-reporting, and corrective actions taken to address noncompliance.
8. With regard to the Dear Healthcare Provider (DHCP) letter sent during the reporting period:
 - a. The date of initial mailing of the DHCP letter to healthcare providers and professional organizations, and the dates of subsequent mailings.
 - b. The number of recipients of the DHCP letter.
 - c. A copy of all documents included in each distribution of the DHCP letter
 - d. Data establishing the date, number and specialty of healthcare providers (HCPs) targeted with the DHCP letter via email; the number and specialty of HCPs who received the email; the number and specialty of HCPs who opened the email; the number of emails that were undeliverable; the number of letters sent via hard copy and the number distributed by sales representatives; the names of professional organizations contacted to distribute the DHCP letter to their members; the names of the organizations that accepted and redistributed the letter; and the names of the professional organizations that declined to accept or redistribute the DHCP letter.
9. An assessment of the percentage of not-yet-trained prescribers who are presented with REMS materials via sales specialists, medical liaisons, or medical information department during the reporting period.
10. An assessment of the number and percentage of unique prescribers who complete the educational training (during the reporting period and cumulative) as defined within the REMS.
 - a. For electronic training completed independently by the HCP, viewing of all module training screens and completion of post-training knowledge assessment questions.
 - b. For training modules delivered in person by VIVUS medical liaison, a statement from the medical liaison that all training materials were reviewed and the post-training knowledge assessment questions were completed.

- c. For print training modules completed independently by the HCP, mailing or faxing a tear-off statement to VIVUS acknowledging full review of materials and completion of the post-training knowledge assessment questions.
11. An assessment of strategies that have been employed during the reporting period to encourage prescribers to undergo educational training.
12. The number and names of certified pharmacies under contract with Vivus for this program, including newly certified pharmacies.
13. A report on any dispensing of Qsymia that occurs outside of certified pharmacies, including the number of instances and the amount dispensed, and corrective actions taken to address the dispensing of Qsymia outside the REMS.
14. The number and names of pharmacies decertified and the reason for the decertification.
15. A report on any distribution of Qsymia that occurs to non-certified pharmacies, including the number of instances, the amount distributed, and corrective action taken to address the distribution of Qsymia to non-certified pharmacies.
16. Data from the reporting period on patients receiving Qsymia including dosage strength prescribed, duration of use, episodes of use per patient, length of break in use for patients with multiple episodes of use.
17. Data on prescribers of Qsymia including the number of unique prescribers prescribing Qsymia.
18. A summary of REMS Call Center activity including frequently asked questions and frequently reported problems.
19. The requirements for assessments of an approved REMS under section 505-1(g)(3) include an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of Qsymia (phentermine and topiramate extended-release) REMS are required at 6 months and 12 months from the date of initial approval of the REMS, and annually thereafter. The first assessment should contain all of the above information with the exception of items 1-5 (i.e., the surveys to ascertain prescribers' and patients' understanding about the safe use of Qsymia and the report based on pharmacy audit). These evaluations should be included in the 12 month assessment and each annual assessment thereafter.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to

the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022580 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022580 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 022580
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022580
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We request that for a period of two years, you submit 15-day alert reports on adverse events classified under the following MedDRA terms: Suicidal and Self-Injurious Behavior (HLT) and Congenital Disorders NOS (HLT), including Congenital abnormality (PT), Teratogenicity (PT), and Multiple congenital abnormalities (PT).

Additionally, we request that you provide analyses of clinical trial and post-marketing reports of serious renal injury, pregnancy exposure, ocular disorders, bone disorders, as well as, events classified under the MedDRA terms: Cognitive disorder (PT), Seizure and seizure disorders NEC (HLT), Substance-related disorders (HLT) [including Intentional drug misuse (PT), Intentional overdose (PT), Dependence (PT), Drug abuse (PT), Drug dependence (PT), Drug withdrawal syndrome (PT), Substance abuse (PT), and Withdrawal syndrome (PT)], Suicidal and Self-Injurious Behavior (HLT), and Congenital Disorders NOS (HLT) [including Congenital abnormality (PT), Teratogenicity (PT), and Multiple congenital abnormalities (PT)] as adverse events of special interest in your periodic safety update reports.

If you have any questions, please call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Package Insert
Medication Guide
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC C COLMAN
07/17/2012