



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 18708/S-018

**SUPPLEMENT APPROVAL**

Questcor Pharma., Inc.  
3260 Whipple Road  
Union City, CA 94587

Attention: David J. Medeiros  
Sr. Vice President, Pharmaceutical Operations

Dear Mr. Medeiros:

Please refer to your supplemental new drug application dated May 27, 2008, received May 27, 2008 for, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doral® (quazepam) 7.5 mg and 15 mg Oral Tablets.

We also acknowledge receipt of your additional amendment dated October 1, 2008 which responded to our request for information relative to the *in-vitro* inhibition study you conducted.

This prior approval labeling supplemental new drug application provides for updated information in the Package Insert regarding results of *in-vitro* study to assess human liver CYP inhibition potential of Doral (quazepam).

As discussed in the July 22, 2009 telecon with you and members of your staff, we have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to, the enclosed labeling (text for the package insert, text for the Medication Guide. These revisions are terms of the NDA approval. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "**SPL for approved NDA 18708/S-018.**"

## **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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

There is no pediatric study requirement for this application because the application does not involve a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

## **POST MARKET REQUIREMENTS UNDER 505(O)**

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (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 (section 505(o)(3)(A)).

Since Doral (quazepam) was approved on December, 27, 1985, we have become aware of the *in vitro* inhibition study that you conducted in which quazepam was found to be a mechanistic inhibitor of CYP2B6. Based on the results of the *in vitro* study, there is a potential for drug interactions between Doral (quazepam) and CYP2B6 substrates, leading to increased exposure to CYP2B6 substrates and resultant adverse events. Therefore, we consider this to be “new safety information” as defined in FDAAA.

There is no adequate information in the literature on extrapolation of *in vitro* data to *in vivo* expectations for mechanism-based inhibition. To fully characterize this signal of a serious risk of adverse events following increased exposure to CYP2B6 substrates, the *in vitro* findings should be assessed further.

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 signal of a serious risk of increased exposure to CYP2B6 substrates.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this signal of a serious risk of adverse events following increased exposure to CYP2B6 substrates.

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

**1510-1.** A drug interaction clinical trial with quazepam and bupropion in extensive metabolizers of CYP 2B6 to characterize the potential serious risk of an interaction.

The timetable you submitted on August 13, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	November 1, 2009
Trial Completion Date:	March 31, 2010
Final Report Submission:	August 31, 2009

Submit the protocols to your IND with a cross-reference letter to this NDA 18708. Submit all final reports to your **NDA 18708**. 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.

### **LETTER TO HEALTHCARE PROFESSIONALS**

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH  
Food and Drug Administration  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

**REPORTING REQUIREMENTS**

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

If you have any questions, call Cathleen Michaloski, MPH, Sr. Regulatory Project Manager, at (301) 796-1123.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director, Division of Neurology Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

Enclosure  
Content of Labeling

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-18708

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SUPPL-18

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QUESTCOR  
PHARMACEUTICA  
LS INC

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DORAL TABLETS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CATHLEEN B MICHALOSKI

09/02/2009

S 18 App

RUSSELL G KATZ

09/04/2009