# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209139Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 119,968

**MEETING PRELIMINARY COMMENTS**

codaDOSE, Inc.
Attention: H. Greg Thomas, PhD
5659 Southfield Drive
Flowery Branch, GA 30542

Dear Dr. Thomas:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Valsartan Oral Solution (4 mg/mL).

We also refer to your October 15, 2013 correspondence, received October 16, 2013, requesting a Pre-IND meeting to discuss the development plans for Valsartan Oral Solution (4 mg/mL) and your intention to submit a 505(b)(2) New Drug Application (NDA).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, please contact me at (301) 796-0510.

Sincerely,

*{See appended electronic signature page}*

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

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**PRELIMINARY MEETING COMMENTS**

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|---|---|
| **Meeting Type:** | B |
| **Meeting Category:** | Pre-IND |
| **Date:** | December 5, 2013 |
| **Time:** | 10:30 – 11:30 AM ET |
| **Phone Arrangements:** | Please provide a CALL-IN NUMBER and PASSCODE to FDA |
| **Application Number:** | PIND 119,968 |
| **Product Name:** | Valsartan Oral Solution (4 mg/mL) |
| **Indication:** | For the treatment of hypertension; for the treatment of heart failure (NYHA class II-IV); in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, to reduce cardiovascular mortality. |
| **Sponsor/Applicant Name:** | (b) (4). |

**Introduction:**
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **December 5, 2013 at 10:30 – 11:30 AM ET** between (b) (4) and the Division of Cardiovascular and Renal Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

## 1.0 BACKGROUND

The sponsor, (b) (4) requested this Pre-IND Meeting to discuss the development plans for Valsartan Oral Solution (4 mg/mL) and their intention to submit a 505(b)(2) New Drug Application (NDA). The sponsor believes this new dosage form will facilitate the correct administration of valsartan in patients who cannot swallow tablets and/or require administration of the drug via nasogastric or other gastronomy tubes. The proposed indications are the same as for Diovan® (valsartan) Tablets, approved under NDA 21-283: for the treatment of hypertension; for the treatment of heart failure (NYHA class II-IV); and in clinically stable patients with left ventricular failure or left ventricular dysfunction following

myocardial infarction, Diovan® is indicated to reduce cardiovascular mortality. The sponsor plans to rely on the demonstration of safety and efficacy for valsartan tablets as approved under NDA 21-283 for Diovan®. The sponsor's Valsartan Oral Solution (4 mg/mL) will have the same active ingredient and route of administration, and will be administered at the same dosage concentration for the same indications as the reference listed drug, Diovan®.

## 2.0 DISCUSSION

### Regulatory

Question 2.1
The Sponsor desires to submit a 505 (b) (2) New Drug Application (NDA) for its proposed Valsartan Oral Solution. Is the Agency in agreement with the 505(b) (2) regulatory pathway for the Valsartan Oral Solution product?

***FDA Preliminary Response:***
A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

Your briefing document references FDA reviewers' public summaries for support of safety and/or efficacy. This is not acceptable because the summaries to not constitute the full reports of investigations (21 CFR 314.430(e)(2)). A 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

| List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature | |
|---|---|
| Source of information<br>(e.g., published literature, name of listed drug) | Information Provided<br>(e.g., specific sections of the 505(b)(2) application or labeling) |
| 1. Example: Published literature | Nonclinical toxicology |
| 2. Example: NDA XXXXXX "TRADENAME" | Previous finding of effectiveness for indication X |
| 3. Example: NDA YYYYYY "TRADENAME" | Previous finding of safety for Carcinogenicity, labeling section XXX |
| 4. | |

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR

314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Question 2.2
The Sponsor intends to reference the approved labeling for the RLD as the sole support for use in patients who are unable to take Valsartan tablets orally, including for the Pediatric Use section, of the 505 (b) (2) application. The proposed labeling will be consistent with the approved labeling for the RLD. Based on 21 C.F.R. § 314.55, the Sponsor will rely on the pediatric use information in the RLD package insert since the proposed Oral Solution product does not represent a new active ingredient, new indication, new dosing regimen or new route of administration. Does the Agency agree with this approach?

***FDA Preliminary Response:***
No, we do not agree. The submission of your NDA will trigger PREA because your proposed oral solution is considered a new dosage form under PREA. The Pediatric Research Equity Act (PREA) requires that all NDAs, BLAs, or supplemental applications for a new active ingredient, new indication, ***new dosage form***, new dosing regimen, or new route of administration contain a pediatric assessment unless a pediatric plan has been submitted and a request for a waiver or deferral has been granted. We remind you that because your application will trigger PREA, you must submit a Pediatric Study Plan (PSP) within 60 days after your End-of-Phase-2 (EOP2) meeting. Guidance on the content of and process for submitting an initial pediatric study plan is available at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf).

Note that the FDA Clinical Pharmacology review included in your background packet states that the doses used in the clinical trial of valsartan for hypertension in patients 1 to 5 years of age may have been too high. We additionally note that doses used in the clinical trial for valsartan for hypertension in patients 1 to 5 years of age suggested evidence of effectiveness but the doses studied may have been too high. Therefore, a clinical trial in pediatric hypertension patients age 1-5 years using a lower dose may be needed. You should submit data to support your rationale for pediatric studies for the relevant pediatric populations for each proposed indication.

We do agree, however, that referencing the Pediatric Use section of the approved labeling for the RLD, Diovan, is acceptable. The safety concern in patients less than 1 year of age must also be reflected in your proposed labeling.

**Clinical Pharmacology**

Question 2.3
The Sponsor intends to submit a BA/BE waiver request for the Valsartan Oral Solution product (4 mg/mL) with the IND application, and supportive data as it meets the provisions established in 21 CFR 320.22. The Sponsor plans to establish similar in vitro dissolution profiles between the Valsartan Oral Solution (4 mg/mL) and the extemporaneously prepared oral suspension (4 mg/mL prepared from eight (8) 80 mg tablets in 160 mL solution) to bridge to clinical data. Does the Agency agree with the proposed BA/BE waiver request?

***FDA Preliminary Response:***
No, we do not agree. Your proposed product and the RLD are different dosage forms. Therefore, in vivo bioequivalence data comparing your proposed drug product to the RLD at the same molar doses are needed to support the approval of your proposed product.

**Clinical**

Question 2.4
As the proposed Valsartan Oral Solution will be administered at the same dosage concentration, for the same duration, and for the same indications as the extemporaneously compounded oral suspension prepared from the RLD, no clinical studies are currently planned. Does the Agency find this approach acceptable?

***FDA Preliminary Response:***
No further clinical studies are required in adults.

**Nonclinical**

Question 2.5
The proposed Valsartan Oral Solution contains excipients on the inactive ingredient guide (IIG) and within the range of concentrations found in previously approved products and does not contain any excipient that significantly affects drug absorption. Therefore, no additional nonclinical studies are proposed. Does the Agency find this approach acceptable?

***FDA Preliminary Response:***
We agree.

**Chemistry, Manufacturing, and Controls**

Question 2.6
The stability studies of the Valsartan Oral Solution drug product will be performed according to ICH guidelines. In addition, comparative degradation studies of Diovan® tablets and extemporaneously prepared suspension (from tablets) will be utilized for comparison of impurity profiles. The stability protocol and proposed studies are provided for review. Please comment as to completeness and acceptability for approval.

***FDA Preliminary Response:***
Quality
Your proposed stability protocol and studies are appropriate. Since you did not specify the container closure system but have proposed ICH storage conditions for semi-permeable containers, you should monitor the loss of water from the filled solution at each test time point.

Propose an identification test that does not rely solely on HPLC retention time, in the drug product specification – see ICH Q6A.

Microbiology
The proposed Microbial release and stability specifications should be expressed in a manner consistent with the recommendation in USP Chapter <1111> - NMT (b) (4) CFU/mL Total Aerobic Microbial Count; NMT (b) (4) CFU/mL Total Combined Yeasts/Molds Count and the Absence of Escherichia coli in (b) (4).

Additionally, antimicrobial effectiveness should be demonstrated during pharmaceutical development studies by performing antimicrobial effectiveness testing (e.g., USP <51>) on a batch of the drug product formulated at, or below, the minimum preservative content specification.

**DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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/s/

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QUYNH M NGUYEN
11/27/2013