CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211759Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211759/Original 1
(b) (4)

REFUSAL TO FILE

codaDOSE, Inc.
5659 Southfield Drive
Flowery Branch, GA 30542

Attention: H. Greg Thomas, PhD
Vice President of Research & Development

Dear Dr. Thomas:

Please refer to your New Drug Application (NDA) dated and received March 9, 2018, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA).

NDA 211759 provides for the use of VYSCOXA (celecoxib) oral suspension, 10 mg/mL for the following indications that, for administrative purposes, we have designated as follows:

- NDA 211759/Original 1 – For use in osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, (b) (4)

(b) (4)

After a preliminary review, we find NDA 211759/Original 1 (b) (4) not sufficiently complete to permit a substantive review. Therefore, we are refusing to file NDA 211759/Original 1 (b) (4) under 21 CFR 314.101(d) for the following reasons:

Clinical

1. The submission lacks an integrated summary of safety (ISS), integrated summary of efficacy (ISE), and a benefit-risk analysis for the product. These sections are required for an NDA submission. Provide these sections. You may cross-reference the clinical summaries of efficacy and safety in Module 2 if these sections contain adequate information.

2. The clinical section is not legible and organized in a manner to allow substantive review. For example, some of the tables in Module 2.7.1 are unclear as there are dashes rather than numbers which appear to indicate that there are no events. Provide the data in an organized manner to allow substantive review. In addition, all documents must be in their final version without track changes.

3. The documents entitled "Summary of Results of Individual Studies" in Module 2 are not consistent with the required discipline summaries since they only include information from individual studies. In addition, these summaries only include tables. Provide the required discipline summaries and provide the information in a manner to allow substantive review.

4. There is no discussion of the relevance of the information intended to provide the scientific bridge between your product and the referenced materials. Provide information to support the relationship between the proposed product and the listed drug/published literature, including a discussion of the comparative bioavailability results (i.e., 51% greater C_{max} and 20% greater AUCs for the proposed oral suspension than Celebrex capsule).

   Given that the product was not bioequivalent to the listed drug, include a description of how this impacts considerations related to efficacy and safety of the proposed product. Given that the product shows an increase in relative systemic exposure compared to the listed product, provide additional information to support the safety of the proposed product. Include copies of all referenced citations in the NDA submission. Translate all journal articles that are not in English into English.

5. There is no safety assessment based on all current worldwide knowledge regarding celecoxib. Provide this information.

6. There is no evaluation of the safety issues that are known to occur with the drugs in the class to which the proposed drug belongs. Provide this information.

7. The proposed pediatric assessment fails to discuss the lack of bioequivalence between the proposed product and listed drug. Submit a discussion of how the increased exposure impacts the proposed pediatric plan.

8. There is no review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) and update the labeling to be compliant with the Pregnancy and Lactation Labeling Rule (PLLR). Provide this information.

9. If foreign data are submitted, provide a rationale for assuming the applicability of foreign data in the submission to the U.S. population.

10. The two submitted clinical pharmacology trials only included male subjects and there is no discussion of how these data are appropriate to support an indication of primary dysmenorrhea. Provide a rationale to explain how the pharmacokinetic data of South Asian males would be applicable to U.S. premenopausal females. Such an explanation may include information to demonstrate that the pharmacokinetic profile of the South Asian men is comparable to that of premenopausal women in the U.S. Alternatively, conduct new bridging PK studies in premenopausal women in the U.S.

11. To establish the safety of the proposed oral suspension for the (b) (4) provide the following:

    a. A summary and analysis of published literature, including copies of individual publications, to support the safety of the new formulation. If available, include all published literature assessing celecoxib for (b) (4).

    b. A summary and analysis of post-marketing pharmacovigilance data such as line-listing data in the FDA's Adverse Events Reporting System (FAERS).

    c. A summary of safety data for the completed clinical pharmacology trials.

Nonclinical

12. The application does not contain a Nonclinical Module 2 and Module 4 and is lacking pharmacology and toxicology information to allow for a substantive review.

    a. Submit nonclinical information that is organized in accordance with current regulations and guidelines for eCTD content and format.

    b. Submit Module 2.6 Nonclinical Written and Tabulated Summaries based on the referenced drug product and a review of the literature since approval of the referenced drug product. Include a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of the proposed drug product. Include copies of all referenced citations in the NDA submission in Module 4. Translate all journal articles that are not in English into English.

    c. In Module 2 of the application (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, how these levels compare to ICH Q3A(R2) and Q3B(R2) qualification thresholds, and if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.

13. The nonclinical sections in the submitted label are not consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). To comply with PLLR content and format requirements, conduct a thorough review and of the available published nonclinical literature on animal reproductive and developmental toxicology studies with celecoxib and provide a summary of these studies along with an integrated summary to inform Sections 8 and 13 of the label. Information on the final rule and links to the FDA draft guidance document are available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

Clinical

1. No adverse events were reported in the clinical pharmacology studies. Provide an assessment of any safety findings (or absence of safety findings) in the completed trials.

Clinical Pharmacology

2. Confirm the final to-be-marketed formulation was used in the comparative bioavailability study (Study 083-17) and food effect study (Study 087-17).

3. Provide justification of the proposed labeling (b) (4) in the context of greater food effect with your product (i.e., 78% increase in C_{max} and 55 - 58% increases in AUCs) than Celebrex capsule (i.e., 10 – 20% in AUCs).

Chemistry, Manufacturing, and Control

4. The acceptance criterion for microbial limits testing per USP (b) (4) for the total (b) (4) count of NMT (b) (4) CFU/mL, which was provided as part of the release and stability specifications of the drug product, is acknowledged. However, this limit exceeds the USP <(b) (4)> recommended acceptance criterion of (b) (4) CFU/mL (maximum acceptable count of (b) (4) for the total (b) (4) count for aqueous preparations for oral use. Modify the acceptance criterion for microbial enumeration of the total (b) (4) count for both the release and stability specifications to be in-line with USP <(b) (4)> guidelines.

5. Confirm that a method verification study for microbial enumeration per USP (b) (4)> was performed with acceptable results.

6. Confirm that method verification studies for absence of specified microorganisms (i.e., for *Escherichia coli, Salmonella* species, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*) per USP <62> was performed with acceptable results.

7. It is acknowledged that the release and stability specifications include a test for (b) (4) with the acceptance criterion of "negative." Additionally, *Method Validation Report for Microbial Assay Suitability Testing of DP 0000.pdf* (Section 3.2.P.5.3) is acknowledged for a description of the validation test method for detection of (b) (4). However, the report lacked details essential for review of the validation test method. Provide a narrative summary of the validation test method that includes a description of the test method, acceptance criteria, and results that demonstrate (b) can be detected if present in the manufacturing process for the drug product.

8. End-point testing for the presence of (b) (4) in the final drug product is acknowledged. However, explain if a risk assessment of potential sources (i.e., raw materials, the manufacturing environment, etc.) for the introduction of (b) (4) into the manufacturing process was performed. If so, indicate potential sources that were identified and describe the steps that were implemented to minimize the risk of (b) (4) organisms in the final drug product. It is recommended that the potential sources be monitored as in-process controls during routine production. Sampling procedures and acceptance criteria for these in-process controls should be established based on the findings of the risk assessment.

9. Provide data (i.e., log reduction data) for antimicrobial effectiveness testing per USP <(b) (4)> performed with drug product containing the lowest acceptable (b) (4) content listed in the release and/or stability specifications (i.e. (b) (4) % of (b) (4) . Additionally, include (b) (4) in your USP <(b) (4)> antimicrobial effectiveness tests to demonstrate preservative suitability against (b) (4).

10. We remind you that as of January 2018, the Heavy Metals (USP <231>) testing was discontinued and the test for Elemental Impurities (USP <232> and USP <233>) is in effect. Update the specification to conform with compendial requirements and/or reporting of Elemental Impurities as outlined in ICH Q3D.

11. Update the stability information in the DMF with all available stability data collected to date for the Long-Term conditions (25 ^{0}C $\pm$ 2 ^{0}C) / 60 % ($\pm$ 5 %) RH.

12. Since the drug product is a suspension, a measure of redispersability is required. It is unclear if the suspension needs to be shaken prior to use or not. If the suspension is intended to be shaken prior to administration, provide data to show uniformity of the suspension after it is shaken, how long the product needs to be shaken to attain uniformity of the suspension and how long the API is suspended before it settles. Content uniformity should be included as a release specification. Viscosity data should be provided as part of the formulation development discussion.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

13. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns. We note the highlights section is not in two-column format, with ½ inch margins between columns.

14. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. We note that the length of the highlights is more than one-half page. Submit a waiver for our review.

15. A horizontal line must separate HL from the Table of Contents (TOC), **and** TOC from the Full Prescribing Information (FPI). We note there is no horizontal line separating HL

from TOC and TOC from FPI.

16. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format. We note that not all the headings are presented in the center of the horizontal line (example: Adverse Reactions and Drug Interactions are not centered).

17. The Boxed Warning (BW) in Highlights must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered. We note the word "and" is not in lower case.

18. A changed section must be listed under the Recent Major Changes (RMC) heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. No listing should be one year older than the revision date. We note the recent major changes are at least one year older than the revision date. These changes must be removed.

19. The TOC should be in a two-column format. We note the TOC is not in a two-column format.

20. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*." We note some of the cross-references in the FPI are not all italicized and does not reference the section. For example, under 2.1 General Dosing Instructions, the entire cross-reference should be italicized and should reference Clinical Pharmacology instead of Pharmacokinetics.

21. The BW section in the FPI must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. We note the word "and" is not in lower case.

Note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file NDA 211759/Original 1 (b) (4) A meeting package should be submitted with this Type A meeting request. To file this NDA 211759/Original 1 (b) (4) over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you do not agree with our conclusions, you may request that NDA 211759/Original 1 (b) (4) be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. NDA 211759/Original 1 (b) (4) will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.'

All future submissions to your NDA should specify the NDA number (b) (4)

If you have any questions, call the responsible Regulatory Project Managers:

For NDA 211759/Original 1 – Sandy Truong at (301) 796-5719
(b) (4)

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

{See appended electronic signature page}

Audrey Gassman, MD
Deputy Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

SHARON H HERTZ
04/30/2018

AUDREY L GASSMAN
04/30/2018