CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209964Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209964

REFUSAL TO FILE

Amgen Inc.
Attention: Christine Kubik
Senior Manager, Regulatory Affairs
601 13th St, NW
12th floor
Washington, DC 20005

Dear Ms. Kubik:

Please refer to your New Drug Application (NDA) dated December 21, 2016, received December 21, 2016, submitted under section 505(b)of the Federal Food, Drug, and Cosmetic Act (FDCA), for Corlanor® (ivabradine) Oral Solution (b) (4) 1.0 mg/mL.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reason:

Ivabradine oral solution is a sterile, unpreserved, aqueous product. FDA has concluded that in order to ensure drug product microbiological quality and safety, the product should be manufactured using validated manufacturing and sterilization processes. The validation information for the drug product sterilization processes has not been provided. Per the 1994 Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, you must provide validation of manufacturing processes at the time of submission.

We note the following review issues identified thus far in our review. Refiling is not contingent upon responses to these issues.

Clinical Pharmacology:

- Please submit the PBPK report that was used to determine starting doses for study CL2-090.

Clinical:

- The November 2012 newsletter states that there were "a few cases of reported study drug misuse". Please provide more details about these cases or tell us where they are described in the application. Please provide all instructions that were given to the investigators that pertained to the oral administration of ivabradine solution. Please

provide all instructions that were given to the subjects that pertained to the oral administration of ivabradine solution.

DMEPA:

Based on the submitted risk analysis, the Division of Medication Error Prevention and Analysis is of the opinion that a Human Factors (HF) validation study is necessary to demonstrate that the intended users can use the product safely and effectively. However, you have not submitted a HF validation study.

Your submitted risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 90 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly.

The following items will facilitate an efficient review of your HF study protocol:

- A summary of preliminary analyses and evaluations, including formative studies;
  - Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis
- An updated risk analysis for your product;
- Detailed HF validation study protocol to include the following elements:
  - Description of intended product users, uses, use environments, and training (if applicable) for commercial product
  - Graphical depiction and written description of product user interface
  - Summary of known use problems with previous models or similar products
  - User task selection, categorization (e.g., critical) and prioritization
  - Validation testing details
    - Objective(s)
    - Type of testing (simulated or actual use)
    - Test environment and conditions of use
    - Training provided to participants and rationale for how it corresponds to real-world training (if applicable)
    - Distinct user groups broken out by number and type of test participants and rationale for how they represent the intended user populations
    - User tasks and use scenarios that will be studied
    - Description of data to be collected and methods for documenting observations and interview responses
    - Methods for root cause analysis of all use errors, difficulties, close calls
    - Definition of performance success and performance failure
    - Moderator transcript

- Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed) that will be tested in the HF validation study
- Five intend-to-market samples of product that will be tested in the HF validation study

The requested information should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:
Applying Human Factors and Usability Engineering to Medical Devices, available online at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published four draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Comparative Analyses and Related Comparative Use Human Factors Studies for Drug-Device Combination Products Submitted in an ANDA and can be found online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf

Considerations in Demonstrating Interchangeability With a Reference Product and can be found online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf

Labeling:

- The length of the Highlights section must be one-half page or less.
- Submit an updated Medication Guide.

- Update the prescribing information to include the newly approved safety language from NDA 206143/ S-002.

Please 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.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

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.'

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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/

NORMAN L STOCKBRIDGE
02/16/2017