DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 210238

NDA APPROVAL

AkaRx, Inc.
c/o Dova Pharmaceuticals, Inc.
Attention: Michelle Rose, PhD
Regulatory Affairs Consultant
240 Leigh Farm Road, Suite 245
Durham, NC 27707

Dear Dr. Rose:

Please refer to your New Drug Application (NDA) dated September 21, 2017, received September 21, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Doptelet® (avatrombopag) tablets, 20 mg.

This new drug application provides for the use of Doptelet® (avatrombopag) tablets for treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.

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.

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 (text for the prescribing information, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on February 20, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 210238**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for avatrombopag was not referred to an FDA advisory committee because this drug is not the first in its class and the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 studies requirement for ages birth to 2 years because necessary studies are impossible or highly impracticable. This is because severe liver disease is extremely rare in children aged less than 2 years.

We are deferring submission of your pediatric studies for ages 2 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act 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)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

PMR 3405-1 Conduct a study in juvenile rats with avatrombopag administration starting on Day 7 post-partum. Dosing duration should be 10 weeks to cover the entire pediatric age range from neonate through adolescence to adulthood. A minimum 4-week recovery period will be included upon completion of dosing to assess reversibility of any adverse effects or delays in development.

The timetable you submitted on May 17, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/31/2018

PMR 3405-2 Conduct a study to evaluate the bioavailability of an avatrombopag age appropriate formulation relative to the 20 mg tablet formulation in the fed condition, and to evaluate the effect of food on the bioavailability of the age appropriate formulation in healthy adults. Subjects should undergo serial blood sampling for avatrombopag plasma concentrations at scheduled intervals during each treatment period.

The timetable you submitted on May 17, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 01/31/2019
Final Report Submission: 07/31/2019

PMR 3405-3 Conduct an open-label study to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of single doses of avatrombopag in pediatric patients (ages 2 to 17 years) with thrombocytopenia associated with liver disease to determine an appropriate dose. Enroll patients to 3 age cohorts: 2 to 6 years, 7 to 11 years, and 12 to 17 years. Patients aged 11 years and younger should receive the age appropriate formulation and patients aged 12 years and older should receive the oral tablet formulation, when appropriate. Subjects should undergo serial blood sampling for avatrombopag plasma concentrations and platelets at scheduled intervals during the study.

The timetable you submitted on May 17, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 07/31/2019
Final Protocol Submission: 10/31/2019
Enrollment Completion: 12/31/2021
Final Report Submission: 04/30/2022

PMR 3405-4 Conduct a study to evaluate the efficacy and safety of once-daily oral avatrombopag for the treatment of thrombocytopenia associated with liver disease prior to an elective procedure in pediatric patients ages 2 to 17 years.

The timetable you submitted on May 17, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/30/2022
Final Protocol Submission:	06/30/2022
Enrollment Completion:	12/31/2026
Final Report Submission:	06/30/2027

Submit the protocols to your IND 076680, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (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.

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 prescribing information, Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, please contact Wan Lee, Regulatory Project Manager, at (240) 402-6583.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling

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

/s/

RICHARD PAZDUR
05/21/2018