DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Mamta Puri-Lechner, PhD
Associate Director, Regulatory Affairs
Arog Pharmaceuticals, Inc
5420 LBJ Freeway, Suite 410
Dallas, TX 75240

RE: (b) (4)
Crenolanib besylate (b) (4)
MA 2

Dear Dr. Puri-Lechner:

As part of its monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed Arog Pharmaceuticals Inc.'s (Arog) booth display for its investigational new drug Crenolanib besylate (b) (4) (Crenolanib) that appeared in the main exhibit hall at the American Society of Hematology's (ASH) 59th Annual Meeting.[1] We have also reviewed a webpage[2] for Crenolanib titled, "Crenolanib A next-gen tyrosine kinase inhibitor for use in FLT3-mutated AML." The booth display and webpage suggest, in a promotional context, that Crenolanib, an investigational new drug, is safe and effective for the purposes for which it is being investigated or otherwise promote the drug. As a result, Crenolanib is misbranded under section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C) Act and in violation of section 301(a) of the FD&C Act. The claims and presentations made on the booth display and webpage are concerning from a public health perspective because they make conclusory representations in a promotional context regarding the safety and efficacy of an investigational new drug that has not been approved by the FDA and whose safety and efficacy have not yet been established.

Background

Crenolanib is an investigational new drug for which there is no marketing authorization in the United States (b) (4)

AML is characterized by the proliferation of myeloid precursors (blasts) with limited ability to differentiate into more mature myeloid cells. These blasts replace normal blood cell-forming tissue in the bone marrow, resulting in decreased numbers of red blood cells, white blood

[1] The ASH Annual Meeting took place from December 9th to 12th, 2017.
[2] Available at https://www.arogpharmaceuticals.com/aml (Last Accessed June 20, 2018)

cells, and platelets. This decrease in normal blood cells results in the symptoms of AML, which is universally fatal without treatment.

Misbranding of an Investigational Drug

Under section 502(f)(1) of the FD&C Act, a drug shall be deemed to be misbranded unless its labeling bears adequate directions for use. Under FDA regulations, adequate directions for use means directions under which the layman can use a drug safely and for the purposes for which it is intended. 21 CFR 201.5. Your booth display and webpage describe the use of Crenolanib in treating AML in general and FMS-like tyrosine kinase-3 (FLT3) positive AML specifically. These uses are ones for which a prescription would be needed because they require the supervision of a physician and, therefore, for which adequate directions for lay use cannot be written.

Although 21 CFR 201.115(b) provides an exemption from the adequate directions for use requirement in section 502(f)(1) of the FD&C Act if a new drug "complies with section 505(i) . . . and regulations thereunder," your investigational drug fails to do so.[3] Among the requirements for the exemption for investigational drugs, 21 CFR 312.7 provides that, "[a] sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution."

The booth display and webpage include claims and presentations that promote Crenolanib as safe and effective for the purposes for which it is being investigated or otherwise promote the drug, including the following:

<u>Booth Display</u>

- Combination Therapy—Future of AML Treatment
  - CRENOLANIB
    - Combinable with chemotherapy at full doses

- Eradicating Activating Mutations
  - CRENOLANIB
    - Potent inhibitor of
      - ✓ FLT3
      - ✓ PDGFRα
      - ✓ PDGFRβ

[3] 21 CFR 201.100 offers another exemption from the requirement for adequate directions for use for prescription drugs provided certain requirements are met; however, Crenolanib does not fall within that exemption because it is an investigational new drug for which there is not marketing authorization in the United States.

Specifically, these claims and presentations suggest that Crenolanib has been established as being safe and effective in treating AML in general when combined "with chemotherapy at full doses." From a public health perspective, this suggestion is especially concerning given the lack of adequate safety and efficacy data about Crenolanib, as well as the toxicity of current chemotherapy regimens and issues regarding the tolerability of such regimens.

Similarly, the suggestion that Crenolanib has established efficacy in "eradicating activating mutations" such as *fms*-like tyrosine kinase-3 (FLT3) is especially troubling given that FLT3 internal tandem duplication (ITD) mutations are associated with a poor prognosis (i.e., increased likelihood of relapse and decreased overall survival).

Additionally, we note that the booth display did not include any information to indicate that Crenolanib is an investigational new drug that has not been approved for commercial distribution in the United States, and that the Crenolanib booth appeared in the main exhibit hall at ASH, alongside approved products.

Webpage

- Crenolanib
  - A next-gen tyrosine kinase inhibitor for use in FLT3-mutated AML

- Crenolanib, a type I TKI, is a potent inhibitor for FLT3-ITD and secondary KD mutants

- THERE ARE SEVERAL ATTRIBUTES THAT SET CRENOLANIB APART FROM OTHER THERAPEUTIC OPTIONS
  1. Crenolanib, whether delivered by itself or as part of a drug combination, has shown benefit in FLT3 mutant AML.
  2. Patients who progress after treatment with prior TKIs may still remain sensitive to crenolanib.
  3. Crenolanib has favorable pharmacokinetics and does not accumulate with repeated dosing.
  4. Crenolanib is a selective type I TKI that does not inhibit wild-type cKIT.

The above claims make numerous conclusory statements about the safety and effectiveness of Crenolanib. For example, the webpage states that Crenolanib is "for use" in FLT3-mutated ALM without including information that Crenolanib is an investigational new drug that has not been approved for any use and states that Crenolanib is a "potent inhibitor for FLT3-ITD and secondary KD mutants," an efficacy claim of clinical benefit that has not been established. Moreover, these claims suggest in a promotional context that Crenolanib, an investigational new drug, has been shown to be different from or superior to other approved therapies for treating AML, and is safe or effective for such uses.

The benefit and risk profile associated with Crenolanib, an investigational therapy, (b) (4) The conclusions made in these claims and presentations may create a misleading impression regarding the usefulness and approval status of this product. From a public health perspective, the claims and presentations are especially concerning given the seriousness of this disease and the relatively few available treatment options.

In summary, the above cited claims and presentations on the booth display and webpage represent the drug as having an established role in the AML treatment paradigm, when Crenolanib has not been proven to be safe and effective within the meaning of the FD&C Act and has not been approved as a drug under that authority for any use.

Conclusion and Requested Action

For the reasons discussed above, Crenolanib is misbranded under section 502(f)(1) of the FD&C Act and in violation of section 301(a) of the FD&C Act. The claims and presentations in the booth display and webpage are concerning from a public health perspective because they make representations in a promotional context regarding the safety and efficacy of an investigational new drug that has not been approved by the FDA.

OPDP requests that Arog immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before July 13, 2018, stating whether you intend to comply with this request, listing all promotional materials for Crenolanib that contain statements such as those described above, and explaining your plan for discontinuing use of such violative materials. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266.** A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g., a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 2 in addition to the (b) (4) in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your materials for Crenolanib comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Rachael Conklin, MS, RN
Regulatory Review Officer
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

{See appended electronic signature page}

Mathilda Fienkeng, PharmD, RAC
Team Leader
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

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/s/

RACHAEL E CONKLIN
06/28/2018

MATHILDA K FIENKENG
06/28/2018