



NDA 208623

NDA APPROVAL

Amicus Therapeutics U.S., Inc.
Attention: Vivian Kessler, RAC
Executive Director, Global Regulatory Affairs
1 Cedarbrook Drive
Cranbury, New Jersey 08512

Dear Ms. Kessler:

Please refer to your New Drug Application (NDA) dated and received December 13, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Galafold (migalastat) capsules, 123 mg.

We also refer to our approval letter dated August 10, 2018, which contained the following error: 150 mg as the strength. The corrected strength is 123 mg.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain August 10, 2018, the date of the original approval letter.

This new drug application provides for the use of Galafold (migalastat) for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (*GLA*) variant based on in vitro assay data.

APPROVAL & LABELING

We completed our review of the application. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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 titled “SPL Standard for Content of Labeling Technical Qs and As” 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

We acknowledge your submission dated July 19, 2018, containing final printed carton labels.

ADVISORY COMMITTEE

Your application for Galafold (migalastat) was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease and outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If post-marketing studies fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your post-marketing requirements specified in your submission dated August 7, 2018. These requirements, along with required completion dates, are listed below.

- 3412-1 A randomized, double-blind, placebo-controlled clinical trial to verify and describe the clinical benefit of Galafold (migalastat) in patients with Fabry disease. The trial will evaluate the efficacy and pharmacodynamic effects (e.g., on plasma lyso-Gb3, alpha-Gal A enzyme activity) of Galafold (migalastat) in patients with a confirmed diagnosis of Fabry disease and amenable, disease-causing *GLA* variants. The trial should be of sufficient duration to observe clinically meaningful changes in Fabry-related symptoms in the intended patient population.

Draft Protocol Submission: 10/2018
Final Protocol Submission: 02/2019
Trial Completion: 08/2025
Final Report Submission: 08/2026

3412-2 A prospective, longitudinal, observational study to evaluate the efficacy and pharmacodynamic effects of Galafold (migalastat) in patients with a confirmed diagnosis of Fabry disease and amenable, disease-causing *GLA* variants. The study will collect, analyze, and compare long-term data on clinical outcomes (major renal, cardiac, and cerebrovascular events) and pharmacodynamic changes (e.g., in WBC alpha-Gal A enzyme activity, plasma lyso-Gb3, serum and urine creatinine, eGFR, urine protein, urine albumin) in treated and untreated patients with Fabry disease and amenable *GLA* variants. The data will be used for the verification and description of the clinical benefit of Galafold (migalastat) in patients with Fabry disease and amenable *GLA* variants.

Draft Protocol Submission:	12/2018
Final Protocol Submission:	04/2019
Study Completion:	04/2030
Interim Report:	10/2023
Interim Report:	10/2026
Interim Report:	10/2029
Final Report Submission:	04/2031

Submit clinical protocols to your IND 68456 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this post-marketing requirement must be clearly designated “**Subpart H Post-Marketing Requirement(s).**”

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct post-marketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We determined that an analysis of spontaneous post-marketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of pregnancy complications, adverse effects on the developing fetus and neonate, and adverse effects on lactation and the breastfed infant. Data are needed on the safe use of Galafold (migalastat) during pregnancy and lactation as there are currently no available human data to inform the safety of Galafold (migalastat) during pregnancy and lactation.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA determined that you are required to conduct the study below.

3412-3 A worldwide, prospective, single-arm, observational study in women exposed to Galafold (migalastat) during pregnancy and lactation to assess: risks of pregnancy complications, adverse effects on the developing fetus and neonate, and adverse effects on lactation and the breastfed infant. Pregnancy exposures and outcomes will be reported voluntarily by providers and patients (e.g., a telephone contact number and/or website will be provided in the product's prescribing information). Complete data will be captured regarding pregnancy outcomes and any adverse effects in offspring. Results will be analyzed and reported descriptively. The study will collect information for a minimum of 10 years. Interim reports on the cumulative findings and analyses will be submitted annually. Data collected retrospectively from other sources will be analyzed separately and reported with the interim and final study reports.

Draft Protocol Submission:	02/2019
Final Protocol Submission:	06/2019
Interim Report:	07/2020
Interim Report:	07/2021
Interim Report:	07/2022
Interim Report:	07/2023
Interim Report:	07/2024
Interim Report:	07/2025
Interim Report:	07/2026
Interim Report:	07/2027
Interim Report:	07/2028
Interim Report:	07/2029
Study Completion:	08/2029
Final Report Submission:	02/2030

Submit the clinical protocol to your IND 68456 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Post-Marketing Protocol Under 505(o), Required Post-Marketing Final Report Under 505(o), Required Post-Marketing Correspondence Under 505(o).**

Submission of the protocol for the required post-marketing observational study to your IND is for purposes of administrative tracking only. The study does not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore is not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically

report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any post-marketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii), provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your post-marketing commitments as follow:

- 3412-4 A PK/PD trial to evaluate an appropriate dosing regimen of Galafold (migalastat) in patients with Fabry disease and amenable *GLA* variants who have severe renal impairment (eGFR < 30 mL/min/1.73m²/year) or who are on kidney dialysis.

The timetable you submitted on August 7, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	11/2018
Final Protocol Submission:	02/2019
Trial Completion:	12/2020
Final Report Submission:	10/2021

- 3412-5 A study to generate additional DNA sequencing data for all recombinant *GLA* cDNA constructs (amenable and non-amenable) used to generate in vitro alpha-galactosidase A (alpha-Gal A) enzyme data from HEK-293 cells in support of NDA 208623. All cDNA constructs must be re-sequenced using additional bi-directional primers internal to the *GLA* cDNA sequence. The newly generated forward and reverse primer sequences should be of sufficient sequence quality and length to provide the necessary base or sequence information that is currently missing from the full length forward and reverse cDNA single strands for all amenable and non-amenable *GLA* variants. The newly generated sequencing data should be appropriately matched and aligned with the previously submitted data in order to complete the bi-directional analysis of the full length of the double-stranded *GLA* cDNA and to produce a consensus *GLA* cDNA sequence for each construct. To confirm the presence of a specific *GLA* variant as well as the base

context of the cDNA, the consensus sequence generated from matched strands from each construct should be compared to the NCBI CCDS reference sequence.

The timetable you submitted on August 7, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	01/2019
Study Completion:	05/2019
Final Report Submission:	11/2019

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 68456 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all post-marketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these post-marketing commitments should be prominently labeled **“Post-Marketing Commitment Protocol,” “Post-Marketing Commitment Final Report,”** or **“Post-Marketing Commitment Correspondence.”**

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved prescribing information (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

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

Alternatively, you may submit promotional materials for accelerated approval products 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>).

REPORTING REQUIREMENTS

We remind you that you must comply with the 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, call LCDR Hong Vu, Regulatory Project Manager, at (301) 796-7401 or Hong.Vu@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling:
Prescribing Information (PI)
Patient Package Insert (PPI)
Instructions for Use (IFU)
Carton Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIE G BEITZ
08/10/2018