CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211996Orig1s000
212161Orig1s000

Trade Name:	Vyndaqel 20 mg Capsule Vyndamax 61 mg Capsules
Generic or Proper Name:	tafamidis meglumine tafamidis
Sponsor:	FoldRx a wholly owned subsidiary of Pfizer, Inc.
Approval Date:	May 3, 2019
Indication:	For the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.

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211996Orig1s000 212161Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211996
NDA 212161

NDA APPROVAL

FoldRx a wholly owned subsidiary of Pfizer, Inc.
Attention: Nancy E Martin, MBA
Senior Director, Orphan Drugs, Worldwide Regulatory Strategy
455 Eastern Point Road
Groton, CT 06340

Dear Ms. Martin:

Please refer to your New Drug Applications (NDAs) dated November 2, 2018, received November 2, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for:

- Vyndaquel (tafamidis meglumine) 20 mg Capsules (NDA 211996).
- Vyndamax (tafamidis) 61 mg Capsules (NDA 212161).

These new drug applications provide for the use of Vyndaquel (tafamidis meglumine) 20 mg Capsules and Vyndamax (tafamidis) 61 mg Capsules for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are 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, Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. 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 CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling 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 (April 2018, Revision 5).* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211996 and NDA 212161**." Approval of theses submissions by FDA are not required before the labeling is used.

ADVISORY COMMITTEE

Your applications for tafamidis meglumine and tafamidis were not referred to an FDA advisory committee because these applications did not raise significant public health questions on the role of the drugs in the diagnosis, cure, mitigation, treatment, or prevention of a disease and outside expertise was not necessary.

REQUIRED PEDIATRIC ASSESSMENTS

Because these drug products for this indication have an orphan drug designation, you are exempt from this requirement.

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 postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse maternal, fetal or infant outcomes resulting from the use of tafamidis or to assess a signal of a serious risk of drug-drug interactions because of tafamidis's potential to inhibit Breast Cancer Resistance Protein (BCRP).

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 has determined that you are required to conduct the following studies:

3576-1 Establish a worldwide pregnancy surveillance study in women exposed to tafamidis meglumine and tafamidis during pregnancy to assess the risks of pregnancy complications and adverse effects on the developing fetus and neonate. The study will collect information for a minimum of 10 years. Provide a complete protocol with details on how pregnancy exposures and outcomes will be captured (e.g., telephone contact number and/or website that will be provided in the

product's prescribing information), and measures to ensure complete data capture on pregnancy outcomes and any adverse effects in the offspring

The timetable you submitted on April 1, 2019 and April 8, 2019 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2019
Final Protocol Submission:	04/2020
Study/Trial Completion:	06/2030
Interim:	04/2021, 04/2022, 04/2023, 04/2024, 04/2025, 04/2026, 04/2027, 04/2028, 04/2029, 04/2030
Final Report Submission:	12/2030

3576-2 Conduct a clinical drug interaction study to evaluate the potential interaction between tafamidis and a relevant BCRP substrate.

The timetable you submitted on April 1, 2019 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	09/2019
Final Protocol Submission:	11/2019
Study/Trial Completion:	05/2020
Final Report Submission:	08/2020

Submit clinical protocol(s) to your IND 071880 with a cross-reference letter to NDA 211996. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to NDA 211996 with a cross reference to NDA 212161. 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 Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

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 postmarketing 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.

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 Package Insert (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 biological products 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 call Maryam Changi, Regulatory Project Manager, at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Ellis Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
  - Patient Labeling
- Carton and Container 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/

ELLIS F UNGER
05/03/2019 06:13:29 PM