

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211996Orig1s000

212161Orig1s000

OTHER REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 26, 2019

TO: Norman Stockbridge, M.D.
Director
Division of Cardiovascular and Renal Products (DCRP)
Office of Drug Evaluation I
Office of New Drugs

Dragos Roman, M.D.
Director (Acting)
Division of Gastroenterology and Inborn Errors
Products (DGEIP)
Office of Drug Evaluation III
Office of New Drugs

FROM: Li-Hong Yeh, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE, OSIS

SUBJECT: Routine inspection of Pfizer Clinical Research Unit,
Brussels, Belgium

1 Inspection Summary

This document is based on a summary of inspectional findings provided by the ORA investigator because the establishment inspection report is pending completion. This review will be amended if the endorsed EIR contains information that impacts my recommendations.

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of studies B3461056 (NDA 212161), B3461054 (NDA 212161), [REDACTED] (b) (4) conducted at Pfizer Clinical Research Unit, Brussels, Belgium.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

After reviewing ORA's inspectional summary, I did not find any issues that could affect the safety of study subjects or reliability of study data. Thus, I conclude that the clinical data from the audited studies B3461056, B3461054, (b) (4) are reliable to support a regulatory decision.

Based on the inspectional summary, clinical data from studies of similar design conducted by Pfizer Clinical Research Unit, Brussels, Belgium between the previous inspection (03/2012) and the end of the current surveillance interval should be considered reliable without an inspection.

2 Inspected Studies:

NDA 212161

Study #1: B3461056
Study Title: "A Phase 1, Open-Label, Randomized, Crossover, Multiple Dose, Pivotal Bioequivalence Study to Compare PF-06291826 4 x 20 mg Tafamidis Meglumine and 61 mgA Tafamidis Free Acid Soft Gelatin Capsules Administered under Fasted Conditions to Healthy Volunteers"
Dates of conduct: 09/20/2017 - 03/01/2018

Study #2: B3461054
Study Title: "A Phase 1, Open-Label, Randomized, Four-Period, Four-Sequence, Single-Dose, Crossover Study in Healthy Volunteers, to Determine the Relative Bioavailability of PF-06291826 61 mgA Tafamidis Free Acid Soft Gelatin Capsules Compared to Commercial 4 x 20 mg Tafamidis Meglumine Soft Gelatin Capsules Administered Under Fasted and Fed Conditions and the Effect of Food on the Oral Bioavailability of PF-06291826 61 mgA Tafamidis Free Acid Soft Gelatin Capsules"
Dates of conduct: 09/29/2017 - 02/23/2018

(b) (4)

ORA investigator [REDACTED] (b) (4) inspected Pfizer Clinical Research Unit, Brussels, Belgium from 04/08/2019 to 04/12/2019.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

3 Inspectional Findings

At the conclusion of the inspection, Investigator [REDACTED] (b) (4) did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

4. Conclusion:

After reviewing ORA's inspectional summary, I did not find any issues that could affect the safety of study subjects or reliability of study data. I conclude that the clinical data from the audited studies B3461056, B3461054, [REDACTED] (b) (4) are reliable to support a regulatory decision.

Based on the inspectional summary, clinical data from studies of similar design conducted by Pfizer Clinical Research Unit, Brussels, Belgium between the previous inspection (03/2012) and the end of the current surveillance interval should be considered reliable without an inspection.

Li-Hong Yeh, Ph.D.
Chemist

Final Classification:

Clinical Site

NAI - Pfizer Clinical Research Unit
Brussels, Belgium
FEI#: 3007000232

cc:

OTS/OSIS/Kassim/ Mitchell/Fenty-Stewart/CDER-OSIS-BEQ
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Yeh
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/
ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov
ORA/OMPTO/OBIMO/Sherri.Rohlf@fda.hhs.gov

Draft: PY 04/25/2019

Edit: RCA 4/25/2019; CB 4/26/2019

ECMS: Pfizer Clinical Research Unit

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881cf8a39>

OSIS File #: BE 8333 (NDA 212161),

(b) (4)

FACTS: 11902272

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/s/

LI-HONG P YEH
04/26/2019 10:46:28 AM

RUBEN C AYALA
04/26/2019 10:49:00 AM

CHARLES R BONAPACE
04/26/2019 11:04:44 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 17, 2019

Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP)

Application Type and Number: NDA 212161 Vyndamax (Tafamidis) and
NDA 211996 Vyndaqel (Tafamidis meglumine)

Product Name and Strength: Vyndamax (Tafamidis) capsules, 61 mg
Vyndaqel (Tafamidis meglumine) capsules, 20 mg

Applicant/Sponsor Name: Foldrx Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
(Pfizer)

FDA Received Date: April 16, 2019

OSE RCM #: 2018-2407-2 and 2018-2384-2

DMEPA Safety Evaluator: Sarah Thomas, PharmD

DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels and carton labeling for Vyndamax and Vyndaqel (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review.^a

2 CONCLUSION

Upon review of the revised container labels and carton labeling for Vyndamax and Vyndaqel, we note that Pfizer revised the "Attention Pharmacist:" statements to include our proposed "NOT substitutable" language. However, Pfizer requested a change from the "mg per mg basis" part of the statement to "per mg basis", so that the statement is consistent with the similar statement found in the prescribing information. Pfizer also requested the removal of the word

^a Thomas S. Labels and Labeling Review Memo for Tafamidis and Vyndaqel (NDA 212161 and NDA 211996). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APRIL 8. RCM Nos.: 2018-2407-1 and 2018-2384-1.

“other” from the Vyndamax “Attention Pharmacist:” statement. Therefore, the final “Attention Pharmacist:” statements will read:

- Attention Pharmacist: Vyndamax is NOT substitutable on a per mg basis with tafamidis meglumine products.
- Attention Pharmacist: Vyndaqel is NOT substitutable on a per mg basis with other tafamidis products.

We find their proposal acceptable.



The revised container labels and carton labeling for Vyndaqel and Vyndamax are acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/

SARAH E THOMAS
04/17/2019 02:32:31 PM

CHI-MING TU
04/17/2019 02:40:26 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 8, 2019

Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP)

Application Type and Number: NDA 212161 Vyndamax (Tafamidis) and
NDA 211996 Vyndaqel (Tafamidis meglumine)

Product Name and Strength: Vyndamax (Tafamidis) capsules, 61 mg
Vyndaqel (Tafamidis meglumine) capsules, 20 mg

Applicant/Sponsor Name: Foldrx Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
(Pfizer)

FDA Received Date: March 28, 2019

OSE RCM #: 2018-2407-1 and 2018-2384-1

DMEPA Safety Evaluator: Sarah Thomas, PharmD

DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels and carton labeling for Vyndamax and Vyndaqel (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review.^a

We note that the [REDACTED] (b) (4) [REDACTED] In addition, we note that Pfizer submitted revised, combined Prescribing Information (PI) labeling which now includes both Vyndamax and Vyndaqel labeling.

^a Thomas S. Labels and Labeling Review for Tafamidis and Vyndaqel (NDA 212161 and NDA 211996). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MARCH 6. RCM Nos.: 2018-2407 and 2018-2384.

2 CONCLUSION

Upon review of the revised container labels and carton labeling for Vyndamax and Vyndaqel, we note that Pfizer incorporated the majority of our recommendations except:

- Pfizer proposed alternative language for the statement that Vyndamax and Vyndaqel are not substitutable on a mg per mg basis, but we disagree with Pfizer's proposal and address this in Section 3 below.
- Pfizer didn't revise the "DOSAGE AND USE(:) See accompanying prescribing information." statement to "Usual Dose: See prescribing information.", because the proposed statement is the standard labeling language used across Pfizer packaging. We find this proposal and rationale acceptable.

Pfizer also asked if they can add the following statement: "The Vyndaqel recommended dosage is 80 mg (four 20 mg tafamidis meglumine capsules) orally once daily." (b) (4)

3 RECOMMENDATIONS FOR PFIZER

We recommend the following be implemented prior to approval of the NDAs:

A. All Carton Labeling

We understand you propose to match the "not substitutable" statement on all carton labeling to the language in the PI (b) (4)

(b) (4)

the intent of the "not substitutable" statement on the carton labeling is to prevent wrong substitution errors by pharmacists during dispensing (i.e., inadvertently dispensing 20 mg capsules for a prescription for the 61 mg capsules due to the "achievable" numerical similarity, $3 \times 20 \text{ mg} = 60 \text{ mg}$). To prevent wrong substitution errors between the two proposed products, we recommend focusing the message on NOT substitutable on a mg per mg basis and so have revised our recommendation to target the attention of pharmacists. Therefore, the word substitutable is the preferred term in this case. Also, we recommend the use of the established name for the other product (b) (4)

- i. Attention Pharmacist: Vyndamax is NOT substitutable on a mg per mg basis with other tafamidis meglumine products.
- ii. Attention Pharmacist: Vyndaqel is NOT substitutable on a mg per mg basis with other tafamidis products.

B. Vyndaqel Carton Labeling

We recommend removing the statement

(b) (4)

Alternatively, relocate the statement to the "Dosage And Use" section on the carton and revise to read "The recommended dosage is 80 mg (four 20 mg tafamidis meglumine capsules) orally once daily. See accompanying prescribing information."

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/s/

SARAH E THOMAS
04/08/2019 04:17:27 PM

CHI-MING TU
04/09/2019 08:34:17 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 29, 2019

To: Maryam K. Changi
Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

Michael Monteleone, Associate Director for Labeling, (DCRP)

From: Zarna Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Sapna Shah, Regulatory Review Officer, OPDP

CC: James Dvorsky, Team Leader, OPDP
Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for VYNDAQEL® (tafamidis meglumine) capsules, for oral administration and TRADENAME (tafamidis) capsules, for oral administration

NDA/BLA: 211996 VYNDAQEL® (tafamidis meglumine) capsules, f or oral administration
212161 TRADENAME (tafamidis) capsules, for oral administration

In response to DCRP consult request dated November 5, 2018, OPDP has reviewed the proposed product labeling (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for VYNDAQEL® (tafamidis meglumine) capsules, for oral administration and TRADENAME (tafamidis) capsules, for oral administration. We note that a second consult request for NDA 212161 was not entered in DARRTS as both NDAs will have the same PI as conveyed to OPDP via email on November 7, 2018, from DCRP (Maryam Changi)

PI and PPI: OPDP's comments on the proposed labeling are based on the draft substantially complete Prescribing Information (draft PI) received by electronic mail from DCRP (Maryam Changi) on March 21, 2019 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under a separate cover on March 28, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 4, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov .

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/s/

ZARNA PATEL
03/29/2019 11:34:14 AM

SAPNA P SHAH
03/29/2019 11:46:42 AM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 29, 2019

TO: Lisa Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
(DMEP)
Office of Drug Evaluation II
Office of New Drugs

Norman Stockbridge, M.D.
Director
Division of Cardiovascular and Renal Products (DCRP)
Office of Drug Evaluation I
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles R. Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of [REDACTED] (b) (4)
[REDACTED]

1. Inspection Summary

OSIS inspected the analytical portion of studies [REDACTED] (b) (4)
[REDACTED]
[REDACTED] B3461056 & B3461054 (NDA 212161, Tafamidis
Meglumine) conducted at [REDACTED] (b) (4)
[REDACTED]

(b) (4) did not observe objectionable conditions and did not issue
Form FDA 483 at the inspection close-out. The final inspection
classification is No Action Indicated (NAI).

1.1. Recommendation

Based on (b) (4) review of the inspectional findings, (b) (4) conclude the data from the audited studies are reliable.

2. Inspected Studies

[REDACTED] (b) (4)

Study B3461056 (NDA 212161)

"A Phase 1, Open-Label, Randomized, Crossover, Multiple Dose, Pivotal Bioequivalence Study to Compare PF-06291826 4 × 20 mg Tafamidis Meglumine and 61 mg A Tafamidis Free Acid Soft Gelatin Capsules Administered Under Fasted Conditions to Healthy Volunteers"

Sample Analysis Period: [REDACTED] (b) (4)

Study B34610564 (NDA 212161)

"A Phase 1, Open-Label, Randomized, Four-Period, Four-Sequence, Single-Dose, Crossover Study in Healthy Volunteers, to Determine the Relative Bioavailability of PF-06291826 61 mg A Tafamidis Free Acid Soft Gelatin Capsules Compared to Commercial 4 × 20 mg Tafamidis Meglumine Soft Gelatin Capsules Administered Under Fasted and Fed Conditions and the Effect of Food on the Oral Bioavailability of PF-06291826 61 mg A Tafamidis Free Acid Soft Gelatin Capsules"

Sample Analysis Period: [REDACTED] (b) (4)

[REDACTED] (b) (4)

3. Scope of Inspection

OSIS scientist [REDACTED] (b) (4) audited the bioanalytical portion of the above studies at [REDACTED] (b) (4)

The previous FDA inspection of [REDACTED] (b) (4) [REDACTED] At the conclusion of the inspection, no deficiencies were observed, and no Form FDA 483 was issued.

The current inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, and sample analysis, and interviews with the firm's management and staff. In addition, Standard Operating Procedures (SOPs), employee training records, laboratory notebooks, audit trails.

To assess the firm's current bioanalytical operations, [REDACTED] (b) (4) examined method validation and study sample analysis of ongoing study 8361-787 (Sotagliflozin and its -O-glucuronide metabolite)

4. Inspectional Findings

[REDACTED] (b) (4)

5. Conclusion

After review of the inspectional findings, [REDACTED] (b) (4) conclude that data from the audited studies are reliable. In addition, data from studies not audited but submitted to pending applications (**Attachment 1**) are reliable for Agency review.

Studies using similar methods conducted between the previous inspection [REDACTED] (b) (4) and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI -

[REDACTED] (b) (4)

cc: OTS/OSIS/Kassim/Choe/Kadavil/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Chennamaneni
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au

Draft: SRC 3/18/2019, 3/21/2019, 3/27/2019
Edit: GB 3/18/2019, 3/20/2019; CRB 3/19/2019, 3/27/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/ANALYTICAL/[REDACTED] (b) (4)
[REDACTED] First
Day of Inspection/Post-Inspection Folder/EIR & EIR Review

OSIS File #: [REDACTED] (b) (4) [REDACTED]

FACTS: [REDACTED] (b) (4)

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/s/

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GOPA BISWAS
03/29/2019 02:21:19 PM

CHARLES R BONAPACE
03/29/2019 02:50:42 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 28, 2019

To: Norman Stockbridge, MD
Director
**Division of Cardiovascular and Renal Products
(DCaRP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Sapna Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): VYNDAQEL (tafamidis meglumine) and TRADENAME (tafamidis)

Dosage Form and Route: capsules

Application Type/Number: NDA 211996 and NDA 212161

Applicant:

Pfizer

1 INTRODUCTION

On November 2, 2018, Pfizer submitted for the Agency's review two original New Drug Applications (NDA) 211996 for VYNDAQEL (tafamidis meglumine) capsules and NDA 212161 for TRADENAME (tafamidis) capsules. The proposed indication for VYNDAQEL (tafamidis meglumine) capsules and TRADENAME (tafamidis) capsules is for the treatment of patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) to reduce (b) (4) cardiovascular-related hospitalization (b) (4) n adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiovascular and Renal Products (DCaRP) on January 3, 2019, November 8, 2018 and November 5, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VYNDAQEL (tafamidis meglumine) capsules and TRADENAME (tafamidis) capsules.

2 MATERIAL REVIEWED

- Draft VYNDAQEL (tafamidis meglumine) capsules and TRADENAME (tafamidis) capsules PPI received on November 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 21, 2019.
- Draft VYNDAQEL (tafamidis meglumine) capsules and TRADENAME (tafamidis) capsules Prescribing Information (PI) received on November 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 21, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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SHAWNA L HUTCHINS
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LASHAWN M GRIFFITHS
03/28/2019 12:41:59 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: March 25, 2019 **Date Consulted:** November 5, 2018

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne Yao, MD, Director
Division of Pediatric and Maternal Health

To: Maryam Changi, PharmD, Regulatory Project Manager (RPM)
Division of Cardiovascular and Renal Products (DCaRP)

Drug: Tafamidis meglumine capsules
Tafamidis capsules

NDA: 211996
212161

Proposed Indication: Reduce (b) (4) cardiovascular-related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM)

(b) (4)

Applicant: Pfizer

Subject: Pregnancy and Lactation labeling as part of original NDA application

Materials Reviewed:

- NDA 211996 and NDA 212161 submitted on November 2, 2018.

Consult Question: DCaRP requests DPMH assistance with the PLLR labeling review for this new molecular entity (NME).

INTRODUCTION

On November 2, 2018, the applicant, Pfizer, submitted a new NDA (211996) for a new molecular entity (NME), tafamidis meglumine, and NDA 212161 for a new dosage form of tafamidis. On November 5, 2018, DCaRP consulted DPMH to provide input on the proper format and content of the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections of tafamidis meglumine and tafamidis labeling to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

REGULATORY HISTORY

- Tafamidis meglumine (NDA 211996) is a stabilizer of transthyretin (TTR) with the following proposed (b) (4)
 - Reduce (b) (4) cardiovascular-related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) (b) (4)
- Tafamidis (NDA 212161) is a new formulation using the free acid form of tafamidis to provide a single oral dosage form.
- Tafamidis meglumine was originally approved in 2011 in the European Union (EU) for the treatment of ATTR in adults with Stage 1 symptomatic polyneuropathy (PN) to delay peripheral neurologic impairment.
- Tafamidis meglumine is currently approved for the treatment of ATTR-PN in 41 countries outside of the U.S.
- Tafamidis meglumine was granted Orphan Drug Designation by the FDA on February 17, 2012.

BACKGROUND

Drug Characteristics¹

- *Drug Class:* stabilizer of transthyretin (TTR)
- *Mechanism of action:* inhibition of TTR tetramer dissociation which inhibits the amyloidogenesis cascade and slows disease progression
- *Dosage and Administration:*
 - Tafamidis meglumine: 80 mg (four 20 mg capsules) oral once daily
 - Tafamidis: 61 mg capsule oral once daily
- *Half-life:* 49 hours
- *Molecular weight:* 503.33 Daltons (tafamidis meglumine), 308.12 Daltons (tafamidis)
- *Plasma protein binding:* >99%

Reviewer's Comment

A single tafamidis 61 mg capsule is bioequivalent to tafamidis meglumine 80 mg (four 20 mg tafamidis meglumine capsules).

¹ Tafamidis meglumine (NDA 211966) and tafamidis (NDA 212161) proposed prescribing information

Condition: Transthyretin amyloidosis (ATTR) and Pregnancy²

- *Description:* a progressive, debilitating, and often fatal, rare disease induced by amyloid fibril deposits of misfolded TTR protein in the peripheral nerves and organs.^{3,4}
- *Etiology:* autosomal dominant inheritance caused by mutation in the TTR gene or by deposition of wild-type TTR protein which leads to the formation of amyloid fibrils.^{5,6} Approximately 100 pathogenic TTR genotypes have been identified.^{7,8}
- *Phenotype:* the major phenotypes of ATTR are ATTR-CM which primarily affects the myocardium (b) (4)
- *Prevalence:*
 - ATTR-CM: rare disease, but no prevalence estimates have been published.⁹ (b) (4)
- *Clinical presentation:* age at onset, form, and rate of progression of disease vary
 - ATTR-CM typically occurs in patients ≥ 60 years who present with symptoms of heart failure (shortness of breath, dyspnea on exertion, orthostatic hypotension, syncope, dysrhythmias).¹¹ (b) (4)
- *Prognosis:*
 - ATTR-CM: fatal disorder, characterized by the deposition of misfolded TTR amyloid fibrils in ventricular walls, causing progressive disruption in the ability of the heart to pump blood through the circulatory system. The mean progression to death is within 2 to 3 years for variants and up to 5 years for wild type.¹² (b) (4)

² Michelle Stewart, et al. Characterizing the High Disease Burden of Transthyretin Amyloidosis for Patients and Caregivers. *Neurol Ther* 2018. 7:349-364.

³ Plante-Bordeneuve V. Update in the diagnosis and management of transthyretin familial amyloid polyneuropathy. *J Neurol*. 2014; 261:1227-33.

⁴ Ruberg FL, et al. Transthyretin (TTR) cardiac amyloidosis. *Circulation*. 2012; 126:1286-300.

⁵ Klabunde T, et al. Rational design of potent human transthyretin amyloid disease inhibitors. *Nat Struct Biol* 2000; 7(4):312-21.

⁶ Saraiva MJ. Transthyretin mutations in health and disease. *Hum Mutat* 1995; 5(3):191-6.

⁷ Connors LH, et al. Tabulation of human transthyretin (TTR) variants, 2003. *Amyloid*. 2003; 10:160-84.

⁸ Benson MD, et al. The molecular biology and clinical features of amyloid neuropathy. *Muscle Nerve*. 2007; 36:411-23.

⁹ Gillmore ID, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. *Circulation* 2016; 133(24):2404-12 (b) (4)

¹¹ Rapezzi C, et al. Transthyretin-related amyloidoses and the heart. *Nat rev Cardiol* 2010; 7 (7): 398-408.

¹² Ruberg FL, et al. Prospective evaluation of the morbidity and mortality of wild type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J* 2012; 164:222-228. E1. (b) (4)

- **Pregnancy:**
 - ATTR-CM: no published reports of pregnancy were identified.
 - ATTR-PN: limited available pregnancy data from the applicant's postmarketing surveillance program are described below (see Table 1 below)

Reviewer's Comment

ATTR-PN occurs during the reproductive years, thus tafamidis exposure in pregnancy is likely in this population. Considering the typical age at diagnosis of ATTR-CM of 60 years is beyond reproductive age (e.g., 15-45 years), it is not unexpected that no pregnancies have been reported in the published literature in patients with ATTR-CM. However, the Clinical Review team noted tafamidis exposure may occur in females of reproductive potential with variant ATTR-CM who can be diagnosed at a younger age. In addition, the Clinical Review Team noted tafamidis exposure may occur during the reproductive years in the genetic offspring of patients with ATTR if treatment is initiated prior to the development of disease manifestations.

REVIEW

PREGNANCY

Nonclinical Experience

Animal reproduction studies in rabbits have shown embryo-fetal toxicity and teratogenicity when administered during organogenesis at exposures equivalent to approximately 9.3 times the AUC at the clinical dose of tafamidis meglumine 80 mg. Postnatal mortality, growth retardation, and impaired learning and memory were observed in offspring of pregnant rats administered tafamidis during gestation and lactation at doses equivalent to approximately 1.8 times the clinical dose of tafamidis meglumine 80 mg on a mg/m² basis. For more details, refer to the Nonclinical Review William Link, PhD.

Applicant's Review of Published Literature

The applicant did not perform a literature search related to tafamidis use and pregnancy.

DPMH's Review of Published Literature

PubMed, Embase, Micromedex¹⁵, TERIS¹⁶, Reprotox¹⁷, and Briggs¹⁸ were searched using "tafamidis" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," and "miscarriage."

- **Micromedex** states "fetal risk cannot be ruled out." It is unknown if tafamidis crosses the placenta. The clinical management recommendations state "advise sexually-active women to use effective contraception during and for at least 1 month after the last dose of treatment. Avoid tafamidis use in pregnant women and women of reproductive potential not using contraception."¹⁹

¹⁵ Truven Health Analytics information, <http://www.micromedexsolutions.com/> Accessed 1/22/19.

¹⁶ TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 1/22/19.

¹⁷ Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 1/22/19.

¹⁸ Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

¹⁹ Product Information: Vyndaqel oral capsules, tafamidis meglumine oral capsules. Pfizer Limited (per EMA), Sandwich, Kent, United Kingdom, 2016

Clinical Trials

Pregnant women were excluded from all clinical trials in the developmental program for tafamidis. The Tafamidis Enhanced Surveillance Pregnancy Outcomes (TESPO) program monitors the pregnancy outcome of women with ATTR-PN exposed to tafamidis during or within 1 month prior to pregnancy. The TESPO program was established to further evaluate the potential risk of reproductive toxicity related to tafamidis exposure as observed in animal studies.

The applicant noted as of June 15, 2018, there have been 22 cases of exposure to tafamidis at the dose of 20 mg per day in patients with ATTR-PN (12 direct maternal exposures; 10 indirect paternal exposures) during or within 1 month of pregnancy. The pregnancy outcomes are summarized below in Table 1. Overall, no congenital malformations have been reported. The applicant stated no further reports of tafamidis exposure during pregnancy have been received spontaneously within the postmarketing experience.

Table 1: Pregnancy Outcomes with Maternal Exposure to Tafamidis Meglumine (dose 20 mg per day)*

Patient ID	Timing of Exposure	Pregnancy Outcome
(b) (6)	Preconception	Live birth
(b) (6)	Unknown	Live birth
(b) (6)	Unknown	Live birth (at term)
(b) (6)	1st trimester	Live birth (at term)
(b) (6)	1 st trimester	Live birth (at term)
(b) (6)	1 st trimester	Live birth (preterm)
(b) (6)	1 st trimester	Spontaneous abortion (8-9 weeks)
(b) (6)	1 st trimester	Spontaneous abortion (19 weeks)
(b) (6)	1st trimester	Induced abortion (twins)
(b) (6)	1 st trimester	Induced abortion
(b) (6)	1 st trimester	Unknown
(b) (6)	1 st trimester	Unknown

*Source: Reviewer's Table

Reviewer's Comment

The above pregnancy cases are limited by the small number of exposed pregnancies with outcome data, and the inability to control for confounders including underlying maternal disease and concomitant use of medications. In addition, these pregnancies were exposed to a lower dose of tafamidis meglumine (20mg) than the proposed dose for approval in the U.S. for ATTR-CM and ATTR-PN (80 mg). Finally, the short duration of drug exposure in pregnancy in these cases (drug discontinued in the 1st trimester at the time of positive pregnancy test) is less than the anticipated chronic exposure to tafamidis for the duration of pregnancy in patients with ATTR. Overall, the limited available pregnancy data have not identified any drug-associated risks for birth defects, miscarriage, or adverse maternal or fetal outcomes.

LACTATION

Nonclinical Experience

Pregnant and lactating female rats were administered repeated daily oral doses of tafamidis meglumine followed by a single oral gavage of radiolabeled tafamidis meglumine on Lactation Day 4 or 12. Radioactivity was observed in milk by 1 hour post-dose and increased thereafter. For more details, refer to the Nonclinical Review by William Link, PhD.

Applicant's Review of Published Literature

The applicant did not perform a literature search related to tafamidis use and lactation.

DPMH's Review of Published Literature

PubMed, Embase, Micromedex²⁰, TERIS²¹, Reprotox²², and Briggs²³, *Medications and Mother's Milk*²⁴, and LactMed²⁵ were searched using "tafamidis" AND "breastfeeding" or "lactation."

- **Micromedex** states "infant risk cannot be ruled out." The clinical management recommendations state "advise women to avoid therapy during breastfeeding."

Clinical Trials

Lactating women were excluded from all clinical trials in the developmental program for tafamidis. The applicant stated there were no reported cases of exposure in lactation.

Reviewer's Comment

Tafamidis meglumine is present in animal milk. There are no available data on the presence of tafamidis meglumine in human milk, the effects on the breastfed infant, or the effects on milk production.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

There were no effects of tafamidis meglumine on fertility, reproductive performance, or mating behavior in the rat at any dose. The paternal and maternal no observed effect level for reproductive toxicity of tafamidis meglumine is greater than 6.9 times the clinical dose. For more details, refer to the Nonclinical Review by William Link, PhD.

Applicant's Review of Published Literature

The applicant did not perform a literature search related to tafamidis use and fertility.

²⁰ Truven Health Analytics information, <http://www.micromedexsolutions.com/> Accessed 1/17/19

²¹ TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 1/17/19

²² Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 1/17/19

²³ Briggs, GG, Freeman, RK, & Yaffe, SJ. (2017). *Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk*. Philadelphia, Pa, Lippincott Williams & Wilkins.

²⁴ Hale, Thomas (2017) *Medications and Mothers' Milk*. Amarillo, Texas. Hale Publishing.

²⁵ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 1/17/19

DPMH's Review of Published Literature

PubMed, Embase, Reprotox¹⁷ were searched using, “tafamidis” AND “fertility,” “infertility,” “contraception,” and “oral contraceptives.” No relevant publications were identified.

Reviewer's Comment

No human data are available to inform the effect of tafamidis meglumine on human fertility. However, animal data do not suggest tafamidis meglumine adversely affects fertility.

DISCUSSION AND CONCLUSIONS

Pregnancy

Limited available human data with tafamidis meglumine use in pregnant women (at a dose of 20 mg per day) have not identified any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no available human data with tafamidis meglumine use in pregnant women at the 80 mg dose. However, animal reproduction studies suggest a potential risk of fetal harm at clinically relevant exposures.

DPMH met with the Nonclinical and Clinical Review teams to discuss the animal reproductive toxicity findings. Considering the limited available human pregnancy data do not support the animal findings but are insufficient to exclude a potential risk to the fetus, DPMH and the Review Team decided to include a “May Cause Fetal Harm” statement in Highlights and subsection 8.1 tafamidis meglumine labeling.

Because of the lack of human pregnancy safety data at the 80 mg dose, potentially concerning animal reproductive toxicity findings, and the anticipated use of tafamidis meglumine in females of reproductive potential with a rare disease, DPMH recommends a pregnancy surveillance study as a postmarketing requirement. This study can likely be incorporated into the Sponsor's established worldwide Tafamidis Enhanced Surveillance Pregnancy Outcomes (TESPO) Program.

Lactation

There are no data on the presence of tafamidis meglumine in human milk, the effects on the breastfed infant, or the effects on milk production. Available data from animal studies indicate tafamidis meglumine is present in rat milk. When a drug is present in animal milk, it is likely the drug will be present in human milk. Based on findings from animal studies which suggest the potential for serious adverse reactions in the breastfed infant, DPMH recommends subsection 8.2 of labeling state breastfeeding is not recommended during treatment with tafamidis meglumine.

Females and Males of Reproductive Potential

DPMH recommends subsection 8.3 of labeling include a contraception heading that describes the potential risk of fetal harm based on findings from animal studies, along with recommendations to consider pregnancy planning and prevention.

RECOMMENDATIONS

DPMH recommends the following:

1. A pregnancy surveillance program PMR with suggested language below:
“Establish a worldwide, (b) (4) study in women exposed to tafamidis meglumine during pregnancy to assess the risks of pregnancy complications and adverse effects on the developing fetus and neonate. (b) (4)

The study will collect information for a minimum of 10 years. (b) (4)

2. DPMH revised Highlights, subsections 8.1, 8.2, 8.3, and section 17 of labeling for compliance with the PLLR (see below). The recommendations below reflect input from the Nonclinical and Clinical Review Teams. DPMH discussed our labeling recommendations with DCaRP on February 14, 2019. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Tafamidis meglumine Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Based on animal studies, may cause fetal harm (8.1)
- Lactation: Advise not to breastfeed (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

 (b) (4)
(b) (4) (see Data). Advise pregnant women of the potential risk to a fetus. Report pregnancies to the Pfizer Adverse Event reporting line at 1-800-438-1985.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data



8.2 Lactation

Risk Summary

There are no available data on the presence of tafamidis meglumine in human milk, the effect on the breastfed infant, or the effect on milk production. Tafamidis meglumine is present in rat milk (*see Data*). When a drug is present in animal milk, it is likely the drug will be present in human milk. Based on the findings from animal studies which suggest the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with tafamidis meglumine.

Data

Pregnant and lactating female rats were administered repeated daily oral doses of tafamidis meglumine (15 mg/kg/day) followed by a single oral gavage of ¹⁴C-tafamidis meglumine on Lactation Day 4 or 12. Radioactivity was observed in milk by 1 hour post-dose and increased thereafter. The ratio of the highest radioactivity associated with ¹⁴C tafamidis meglumine in milk (8 hours post-dose) vs. plasma (1 hour post- dose) was approximately 1.6 on Day 12, indicating tafamidis meglumine is transferred to milk after oral administration.

(b) (4)

8.3 Females and Males of Reproductive Potential Contraception

(b) (4)

17 PATIENT COUNSELING INFORMATION

Pregnancy

Report pregnancies to the Pfizer Adverse Event reporting line at 1-800-438-1985. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Lactation

Advise females not to breastfeed during treatment with tafamidis meglumine [*see Use in Specific Populations (8.2)*].

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/s/

KRISTIE W BAISDEN
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TAMARA N JOHNSON
03/25/2019 04:34:57 PM

LYNNE P YAO
03/25/2019 04:37:47 PM

Division of Neurology Products (DNP) Clinical Consult Memo

NDA	211996
Sponsor:	FoldRX/Pfizer
Drug:	Tafamidis meglumine
Proposed Indication:	ATTR cardiomyopathy (b) (4)
Material Submitted:	NDA submission
Consult Request Date:	12/28/2018
Date Review Completed:	3/14/2019
Clinical Reviewer/Team Leader:	Teresa Buracchio, M.D.
Division Director:	Billy Dunn, MD

Background:

The applicant submitted a New Drug Application (NDA) on November 2, 2018, based on a single trial for tafamidis meglumine for the treatment of “wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM)”. (b) (4)



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**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates**

Date: 3/11/19

Reviewer: Margie R. Goulding, PhD
Division of Epidemiology II

Team Leader: Efe Eworuke, PhD, MSc., B.Pharm
Division of Epidemiology II

Deputy Division Director: Lockwood Taylor, PhD, MPH
Division of Epidemiology II

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Names (Application #): Tafamidis Meglumine 20 mg oral capsules (NDA 211996)
Tafamidis Free Acid 61 mg oral capsules (NDA 212161)

Applicant/sponsor: FoldRx Pharmaceuticals (a subsidiary of Pfizer)

OSE RCM #: 2019-441 (For safety signal assessment for the NDAs)

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Products

NDA 211996 is being reviewed for **tafamidis meglumine 20 mg** (an orphan drug) for the proposed (b) (4) to reduce (b) (4) cardiovascular related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM), (b) (4). It is an oral medication administered once daily. ATTR-CM (b) (4) slowly progressive, debilitating, adult-onset conditions caused by the deposition of transthyretin amyloid fibrils in the myocardium and nerves, respectively. These conditions are caused by either an autosomal dominant inherited mutation in the TTR gene or by deposition of wild-type TTR protein which leads to the formation of amyloid fibrils. ATTR-CM is considered rare, but no prevalence estimates have been published, (b) (4). The deposition occurs when wild type or variant transthyretin becomes unstable and misfolds. Tafamidis selectively binds and stabilizes transthyretin thereby inhibiting tetramer dissociation into monomers, the rate limiting step in the genesis of amyloid.

Another NDA for an alternate oral capsule formulation, **tafamidis free acid 61 mg**, for the ATTR-CM indication, is being reviewed simultaneously. (Taking one 61 mg tafamidis free acid capsule will be more convenient for patients than taking the proposed dose of four 20 mg tafamidis meglumine capsules for ATTR-CM.) The 20 mg tafamidis meglumine capsule NDA was submitted before the 61 mg free acid NDA most likely because the 20 mg capsule is already approved in Europe and being marketed for once daily dosing to treat transthyretin amyloidosis in adults with stage 1 symptomatic polyneuropathy (ATTR-PN).

This review memo covers both tafamidis meglumine and tafamidis free acid products.

1.2. Describe the Safety Concern

Animal studies of tafamidis have shown reproductive toxicity. Developmental reproductive toxicity studies demonstrated increased incidence of skeletal malformations and variations in rabbits at exposure levels in the therapeutic range. Post-natal mortality and developmental anomalies were also observed in rats at dose levels ≥ 12 -times the clinical dose. There are no adequate and well-controlled studies in pregnant women.

The prescribing information will describe this risk in the Highlights section (“Pregnancy: Based on animal studies, may cause fetal harm.” (b) (4))

Although the patient population expected to be exposed to tafamidis may be small, it is possible that

females of reproductive age could be exposed. During clinical development of tafamidis (20 mg) only one patient on tafamidis became pregnant, after discontinuing birth control. Tafamidis was immediately discontinued, the pregnancy was uneventful, and the patient delivered a healthy baby. The patient had received six months of treatment when a routine pregnancy test was positive. Tafamidis exposure prior to its discontinuation was estimated as occurring during the first six weeks of gestation.

Tafamidis meglumine (Vyndaqel) was approved for treating ATTR-PN in the European Union (EU) in Nov. 2011, rejected by FDA in 2012, and approved in Japan in 2013. However, the post-marketing data on tafamidis-exposed pregnancy outcomes is very limited. The EU post-marketing “Tafamidis Enhanced Surveillance for Pregnancy Outcomes” (TESPO) program implemented in 2011 for follow-up of patients taking the 20 mg tafamidis product identified 12 pregnancies that resulted in two miscarriages, two terminations, two unknown outcomes, and six live births with no malformations and no adverse developmental effects in the offspring at up to one year of age.¹

The US labeling will have to describe the safety concern in conformity with the Pregnancy and Lactation Labeling Rule (PLLR), (b) (4)

Note: Tafamidis’ long half-life of approximately 55 hours means that exposure during pregnancy can occur even if the tafamidis has been discontinued, i.e. if the pregnancy starts shortly after the tafamidis is stopped. The product label DPMH favors would say in section 8.3.

**Females and Males of Reproductive Potential
Contraception**

(b) (4)

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an “X” in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women

¹ From M. Goulding’s direct communications with a Division of Pediatric and Maternal Health (DPMH) reviewer on Feb. 20-21, 2019. The DPMH reviewer aggregated these data from the Sponsor’s Oct. 2018 Integrated Summary of Safety.

- No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† *If checked, please complete*

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify: Enhanced pregnancy surveillance program.

Note: The distinctions between a pregnancy registry and a pregnancy surveillance program are:

Pregnancy Registry:

- For medical products with high likelihood of use by females of reproductive potential,
- Sample size should be big enough to detect a difference between the exposed & control groups (internal control group preferred)

Pregnancy Surveillance Program:

- Used when a prospective observational pregnancy cohort study is not feasible
- Can enroll prospective & retrospective cohorts
- Data collected at various timepoints during a pregnancy and infants are generally followed for 12 months
- Can be included within a disease or drug-based registry as is usually the case with drugs for rare diseases.

2.4. Which are the major areas where ARIA is not sufficient, and what would be needed to make ARIA sufficient?

- Study Population
- Exposures
- Outcomes
- Covariates
- Analytical Tools

For any checked boxes above, please describe briefly:



Click here to enter text.

Analytic Tools: ARIA Analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

The outcomes of interest include (*may not be treated medically & captured in medical care claims):

Pregnancy outcomes: miscarriage*, abortion*, delivery,

Birth outcomes: still birth*, (full-term/preterm) live birth,

Live birth outcomes: normal, birth defect (malformation, anomaly), other neonatal problem, gestational age at birth, Apgar score, birth weight, length, head circumference,

Infant developmental delays*, Infant death*

2.5. Please include the proposed PMR language in the approval letter.

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Draft language:



(b) (4)

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/s/

MARGIE R GOULDING
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LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 6, 2019
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 212161 (Tafamidis) and NDA 211996 (Vyndaqel)
Product Name and Strength:	Tafamidis capsules, 61 mg Vyndaqel (Tafamidis meglumine) capsules, 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Foldrx Pharmaceuticals Inc., a subsidiary of Pfizer Inc. (Pfizer)
FDA Received Date:	For NDA 212161: November 2, 2018, December 11, 2018, For NDA 211996: November 2, 2018, December 28, 2018, and February 4, 2019
OSE RCM #:	2018-2407 and 2018-2384
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As a part of the NDA review process, this review evaluates the proposed tafamidis and Vyndaqel container labels and carton labeling, as well as the proposed Prescribing Information (PI) and patient information for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that although the tafamidis 61 mg capsule and Vyndaqel (tafamidis meglumine) 20 mg capsule (equivalent to 12.2 mg tafamidis) are bioequivalent, they are not substitutable on a mg per mg basis. This presents a potential risk for wrong dosing medication errors because healthcare providers may be misled to think 5 tafamidis meglumine capsules at “12.2 mg” of tafamidis approximately equals to one 61 mg tafamidis capsule. We expressed this concern to the review team on February 1, 2019. The review team responded on February 4, 2019 and February 5, 2019 with recommendations to minimize the prominence of the equivalency statement on the labels and labeling and to add a warning against inappropriate substitution of tafamidis and Vyndaqel on a mg per mg basis. We provide related recommendations in Section 4 below.

Also, we did not locate

(b) (4)

Our examination of the submitted tafamidis and Vyndaqel mock-up samples found lack of perforation on the text side of the 10-count blister cards, which makes it difficult for the end-user to tear off a blister cell and obtain a capsule for dosing. We notified the review team on January 31, 2019 and

February 6, 2019 [REDACTED] (b) (4) lack of perforation. We defer to the review team on the determination of the [REDACTED] (b) (4) for the proposed packaging configurations.

Our review of the proposed container labels and carton labeling, as well as the proposed PI and patient information for tafamidis and Vyndaqel identified areas where the labels and labeling may be improved to promote the safe use of the product.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container labels, carton labeling, PI, and patient information for the proposed tafamidis and Vyndaqel may be improved to promote the safe use of the products as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI), tafamidis

1. How Supplied/Storage and Handling Section

- a. Clarify the package configuration descriptions in Section 16 to indicate clearly the number of blister cards and capsules per carton and the number of capsules contained in one blister card, as follows:
 - i. Carton of 3 blister cards. Each blister card contains 10 capsules. (30 capsules total)

[REDACTED] (b) (4)

B. Prescribing Information (PI), Vyndaqel

1. Dosage and Administration Section, Highlights and Full PI

- a. Add the statement "A single TRADENAME 61 mg capsule is bioequivalent to Vyndaqel 80 mg (four 20 mg Vyndaqel capsules). TRADENAME and Vyndaqel are NOT substitutable on a mg per mg basis [see *Clinical Pharmacology (12.3), Clinical Studies (14)*]."

2. Dosage Forms and Strengths, Full PI

- a. To prevent confusion and dosing errors where healthcare providers

[REDACTED] (b) (4)

[REDACTED] from Section 3 of the full PI.

3. How Supplied/Storage and Handling Section

- a. Clarify the package configuration descriptions in Section 16 to indicate clearly the number of blister cards and capsules per carton and the number of capsules contained in one blister card, as follows:
 - i. Carton of 3 blister cards. Each blister card contains 10 capsules. (30 total capsules)

[REDACTED] (b) (4)

- iii. Carton of 4 intermediary cartons. Each intermediary carton contains 3 blister cards. Each blister card contains 10 capsules. (120 total capsules)

4.2 RECOMMENDATIONS FOR PFIZER

We recommend the following be implemented prior to approval of both NDA 212161 AND NDA 211996:

- A. General Comments (Tafamidis and Vyndaqel Container Labels & Carton Labeling)
 1. We note that the established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors including typography, layout, contrast and other printing features in accordance with 21 CFR 201.10(g)(2).
 2. In order to avoid confusion regarding how many mg of tafamidis or Vyndaqel are contained in each capsule versus each blister card, we recommend expressing the strengths as “61 mg per capsule” and “20 mg per capsule” on the container labels and carton labeling.^a
 3. For all carton labeling [REDACTED] (b) (4), in order to mitigate the risk of inadvertent substitution between tafamidis and Vyndaqel on a mg-to-mg basis, we recommend adding a warning to the principal display panel (PDP) of the carton labeling [REDACTED] (b) (4) stating that tafamidis and Vyndaqel are not substitutable on a mg per mg basis:
 - a. Attention: TRADENAME is NOT substitutable on a mg per mg basis with other tafamidis meglumine products.
 - b. Attention: Vyndaqel is NOT substitutable on a mg per mg basis with other tafamidis products.
 4. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling. The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>.
 5. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.^b

6. Revise the following statements on the container labels and carton labeling, “DOSAGE AND USE(:) See accompanying prescribing information.” to the following: “Usual Dose: See prescribing information.”
- B. Tafamidis Container Label, 10 capsule count blister card
1. Revise the order of presentation of the established name with dosage form and strength from “TRADENAME 61 mg (tafamidis) capsules” to^c
TRADENAME
(tafamidis) capsules
61 mg per capsule
- C. Tafamidis Carton Labeling
1. Adequate blank open space should be available to allow the pharmacy to affix the prescription label without interference with other critical information on the packaging. Consider adding a visual indicator (e.g., box with language “place pharmacy label here”) on the carton labeling to indicate to the end-user where the pharmacy prescription label should be affixed to the carton labeling.
 2. Revise the net quantity statements on the tafamidis carton labeling to include the total number of capsules per carton, the total number of blister cards per carton, and total number of capsules per blister card, as follows:
 - a. Contains: 30 capsules per carton. Each carton contains 3 blister cards. Each blister card contains 10 capsules.
 (b) (4)
- D. Vyndaqel Container Label, 10 capsule count blister card
1. Revise the order of the presentation of the established name with dosage form and strength “Vyndaqel 20 mg* (tafamidis meglumine) capsules” to^c
Vyndaqel
(tafamidis meglumine) capsules
20 mg per capsule*

^b Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

^c Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

2. Remove the quantity statements [REDACTED] (b) (4)

E. Vyndaqel Carton Labeling

1. Adequate blank open space should be available to allow the pharmacy to affix the prescription label without interference with other critical information on the packaging. Consider adding a visual indicator (e.g., box with language “place pharmacy label here”) on the carton labeling to indicate to the end-user where the pharmacy prescription label should be affixed to the carton labeling.
2. Revise the net quantity statements on the tafamidis meglumine carton labeling to include the total number of [REDACTED] (b) (4) per carton, the total number of blister cards per carton, and total number of [REDACTED] (b) (4) per blister card as follows:
 - a. Contains: 30 capsules per carton. Each carton contains 3 blister cards. Each blister card contains 10 capsules.
[REDACTED] (b) (4)
 - c. Contains: 120 capsules per carton. Each carton contains 4 intermediary cartons. Each intermediary carton contains 3 blister cards. Each blister card contains 10 capsules.

We also recommend removing the [REDACTED] (b) (4)

[REDACTED] The net quantity statement should appear on the PDP but should be separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded).^c

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/s/

SARAH E THOMAS
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Medical Officer's Review of NDA 211996
Ophthalmology Consult

NDA 211996 Submission Date November 2, 2018
Consult Review Consult Request Date: January 17, 2019
 Review completed: February 12, 2019

Product Name: Tafamidis meglumine

Sponsor: FoldRx a wholly owned subsidiary of Pfizer, Inc.

Requested: Pfizer submitted this 505(b)(1) New Drug Application, 211996, for tafamidis meglumine for the reduction of (b) (4) cardiovascular related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) on November 2, 2018. The clinical data forming the basis for this indication is from the 30-month pivotal study B3461028 comparing tafamidis 20 mg vs. 80 mg vs. placebo. Tafamidis was granted Orphan Designation for the treatment of symptomatic ATTR cardiomyopathy (ATTR-CM) on February 17, 2017. The drug was also granted Fast Track Designation and Breakthrough Designation for this indication on May 17, 2017, and May 18, 2018, respectively.

We identified a safety signal for lens disorder/cataract. There was a higher incidence of these adverse events in both tafamidis groups compared to the placebo group in the pivotal trial (see the attached file for the relevant information about this signal). Negative findings were found in ophthalmic examinations in animals. We would like to get your input on whether this signal could be drug-related considering the event rate, time-course and patient population.

EDR link: \\CDSESUB1\evsprod\NDA211996\211996.enx

Please see attached slides.

Safety Signal #7: Lens disorder/cataract
Signal detected by both SMQ and ODE1-query

	Tafamidis 20 mg (N = 88)	Tafamidis 80 mg (N = 176)	Placebo (N = 177)	Risk Diff T20 mg vs. P	Risk Diff T80 mg vs. P
Lens disorders (SMQ)	7 (8.0%)	18 (10.2%)	6 (3.4%)	4.6	6.8
Cataract	3 (3.4%)	9 (5.1%)	2 (1.1%)		
Vision blurred	2 (2.3%)	5 (2.8%)	3 (1.7%)		
Visual impairment	2 (2.3%)	3 (1.7%)	1 (0.6%)		
Visual acuity reduced	0	1 (0.6%)	0		

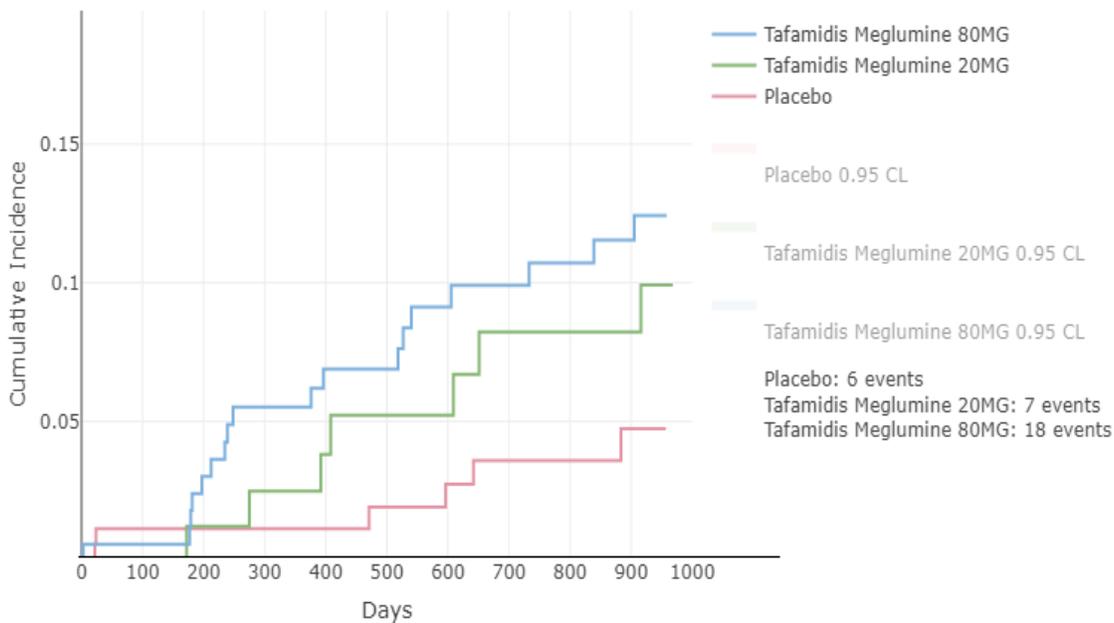
Incidence and event rate for eye disorders

Eyes disorder AEs ^a	n (%)	Event Rate (95% CI)	Rate Difference (95% CI)	Rate Ratio (95% CI)
Placebo (N=177)	6 (3.4%)	1.83		
Tafamidis Meglumine 20MG (N=88)	7 (8.0%)	3.96	2.13 (-1.15,5.41)	2.17 (0.73, 6.45)
Tafamidis Meglumine 80MG (N =176)	18 (10.2%)	5.27	3.45 (0.60,6.29)	2.88 (1.14, 7.27)
Tafamidis 20 mg + 80 mg (N=264)	25 (9.5%)	4.83	3.00 (0.61,5.39)	2.64 (1.08, 6.43)

^ainclude cataract, vision blurred, visual impairment, visual acuity reduced

^bper 100 patient- years

K-M curves for eye disorder AEs



Reviewer's Comment: *I have reviewed all of the reported ophthalmic disorders and re-categorized them as needed. While cataracts can cause vision blurred, visual impairment, and visual acuity reduced in this patient population, it is not accurate to collapse these events into a single category since many of the patients have had their cataracts removed. A summary is provided below:*

Adverse event	Percentage of Patients with Event		
	Placebo (n=177)	20 mg (n=88)	80 mg (n=176)
Cataract	1%	3%	5%
Blurred vision	2%	2%	3%
Dry Eye	3%	1%	3%
Conjunctival hemorrhage	2%		1%
Eye infection	1%		1%
Impaired vision			1%
Vitreous detachment			1%
Retinal Tear		1%	1%
Stye	1%		1%
Blepharochalasis			1%
Epiretinal membrane			1%
Eye contusion			1%
Eye edema			1%
Irritated eye			1%
Ocular hyperemia/itching			1%
Macular degeneration		3%	
Diplopia	1%	2%	
Visual Field Defect		2%	
Glaucoma	1%	2%	
Basal cell carcinoma		1%	
Papilledema		1%	
Eyelid injury	1%		
Amaurosis fugax	1%		
Blepharitis	1%		
Decreased vision	1%		
Pterygium	1%		

Reviewer's Comment: *Of note is the numerically larger number of cataract reports in the 80 mg compared to the 20 mg dose and the placebo. However, the population involved in this study is predominately in the age range that would be expected to develop cataracts (1st quartile reporting adverse reactions=72, 3rd quartile reporting adverse reactions=80). Two of the subjects in the 80 mg group who reported cataracts were noted to have a history of cataracts at baseline. One of the subjects in the placebo group who reported cataracts was noted to have a history of cataracts at baseline.*

The frequency of cataracts or cataract surgery at baseline in each group was:

	Placebo (n=177)	20 mg (n=88)	80 mg (n=176)
Percentage of patients with Baseline Cataract	19%	18%	19%

The percentage of patients with cataracts or patients who have undergone cataract surgery is significantly greater than (approximately 4 times) the reported rate of cataract development. It is expected that there is significant variability around these percentages because ophthalmic examinations have not been routinely performed.

After adding the adverse events which occurred during the clinical trial and subtracting the cases of cataracts which were present at the start of the clinical trial, the differences between groups is small.

	Placebo (n=177)	20 mg (n=88)	80 mg (n=176)
Incidence of Cataracts/Cataract Surgery at the end of the clinical trial	20%	22%	23%

Conclusions: Based on the background rate of cataract development in the patient population studied (consistent with cataract incidence rates in patients of comparable ages) in the submitted clinical trial, the incidence of ocular adverse events including cataract development is not believed to be a signal of a drug-related adverse event.

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

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/

WILEY A CHAMBERS
02/12/2019 10:35:14 AM