

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211996Orig1s000**

**212161Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**Recommendation:** **APPROVAL**

**NDA 211996  
Review #01**

Drug Name/Dosage Form	Tafamidis Meglumine Capsules
Strength	20 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	FoldRx a wholly owned subsidiary of Pfizer, Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
<i>Rolling Part 1 (SD 1)</i>	30-AUG-2018	<i>Amendment (SD 18)</i>	31-JAN-2019
<i>Rolling Part 2 (SD 2)</i>	20-SEP-2018	<i>Amendment (SD 20)</i>	04-FEB-2019
<i>Original (SD 5)</i>	02-NOV-2018	<i>Amendment (SD 21)</i>	15-FEB-2019
<i>Amendment (SD 12)</i>	27-DEC-2018	<i>Amendment (SD 22)</i>	19-FEB-2019
<i>Amendment (SD 13)</i>	28-DEC-2018	<i>Amendment (SD 25)</i>	11-MAR-2019
<i>Amendment (SD 16)</i>	28-JAN-2019	<i>Amendment (SD XX)</i>	

**Quality Review Team**

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Charles Jewell		ONDP
Drug Product	Mariappan Chelliah	Wendy Wilson-Lee	
Labeling			
Environmental	James Laurenson		
Manufacturing	Frank Wackes	Ying Zhang	OPF
Biopharmaceutics	Kaushalkumar Dave	Jing Li	ONDP
OPPQ	Jibril		
Regulatory Business Process Manager	Grafton Adams		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

## Quality Review Data Sheet

**1. RELATED/SUPPORTING DOCUMENTS**

**A. DMFs:**

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	Catalent Pharma Solutions LLC	(b) (4)	Adequate		

**B. Other Documents: *IND, RLD, or sister applications***

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	71880	Tafamidis meglumine for treatment of TTR familial amyloid cardiomyopathy
IND	74866	Tafamidis meglumine for treatment of TTR familial amyloid polyneuropathy
NDA	202737	Tafamidis meglumine capsules for treatment of transthyretin amyloidosis in adult patients with symptomatic polyneuropathy
NDA	212161	Tafamidis capsules for treatment of TTR amyloid cardiomyopathy

**2. CONSULTS**

None.

## Executive Summary

### I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of Tafamidis Meglumine Capsules, 20 mg.

### II. Summary of Quality Assessments

#### A. Product Overview

FoldRx seeks approval of tafamidis meglumine soft gelatin capsules under NDA 211996 for the reduction of (b) (4) cardiovascular-related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) under the 505(b)(1) pathway. ATTR-CM is a rare and fatal disorder. There are no FDA-approved treatments for ATTR-CM. FDA granted orphan designation for a slightly different indication in February 2017. FDA granted fast track designation in May 2017 and breakthrough therapy designation in May 2018. Based on the statistically significant clinical trial results, FDA granted priority review and request that the review team expedite reviews. A sister NDA was also submitted for a tafamidis free acid soft gelatin capsule product (NDA 212161).

The drug product is a soft gelatin capsule containing 20 mg tafamidis meglumine, equivalent to 12.2 mg tafamidis free acid. The product is formulated as a suspension in (b) (4) The proposed dose recommendation is 80 mg (b) (4) administered as four, 20 mg capsules daily. (b) (4)

(b) (4)

(b) (4) FoldRx indicated in the submission that all other quality attributes and process parameters identified as non-critical are controlled through the Pfizer and Catalent quality systems.

The initial risk assessment identified content uniformity, (b) (4) physical stability, and dissolution as moderate risks. The drug product contains a low drug substance load. The drug substance's low solubility (b) (4) increase the risk to physical stability and dissolution. A control strategy for (b) (4)

<b>Proposed Indication(s) including Intended Patient Population</b>	<i>for the reduction of (b) (4) cardiovascular-related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy</i>
<b>Duration of Treatment</b>	<i>Chronic</i>
<b>Maximum Daily Dose</b>	<i>80 mg</i>
<b>Alternative Methods of Administration</b>	<i>None</i>

**B. Quality Assessment Overview**

Tafamidis Meglumine is proposed for manufacture for commercial use at the Pfizer Ringaskiddy Site (Ireland) using the development “Process D” optimized for commercial use. Early studies (toxicological and clinical studies) were performed on material manufactured at other sites, using processes at various stages of development, known as A1, A2, A3 and A4. Process D material was used in most clinical studies. The Process D material is of equivalent quality or better than the process A materials. The optimized process is (b) (4)

(b) (4)

Process D was assessed as an adequately understood process and generates no impurities greater than the qualification threshold described in ICH Q3A. There is only one specified impurity (a process impurity and degradation product) and it is limited to NMT (b) (4)%. All other known impurities are controlled as an unspecified impurity, NMT (b) (4). The analytical method is validated to detect all impurities known or determined to occur using stressed stability study data. Levels of meglumine are also determined by a validated method, to limit meglumine to (b) (4) ratio with tafamidis free acid.

Adequate stability studies were performed on tafamidis meglumine in representative container closure systems, the studies support stability; there was no observed degradation for (b) (4) months, when stored at (b) (4). The drug substance is demonstrated not to be sensitive to light-based degradation. A retest period of (b) (4) months is designated for this drug substance by the FDA (concurrence with the applicant’s request).

Tafamidis meglumine exists as one known (b) (4) polymorph (b) (4)

(b) (4) Tafamidis meglumine is poorly soluble in water and non-hygroscopic. (b) (4) This supports

manufacturability of the drug product, a suspension (b) (4), used to filled soft gel capsules.

Tafamidis meglumine 20 mg will be provided as size 9.5 soft gelatin capsules. It is formulated as drug substance suspended in (b) (4)

(b) (4) The capsules are manufactured by (b) (4) and the CMC information for the soft gelatin capsule shell is cross-referenced to (b) (4) DMF (b) (4). The controls for all the excipients are adequate and the excipients are qualified.

The proposed specification is adequate to control the quality of the drug product. The controls for impurities meet ICH Q3B(R2). The Applicant adequately validated all non-compendial analytical methods used in the drug product testing. Drug substance for the primary stability batches were supplied by (b) (4) For the supporting stability batches, they were supplied by Pfizer Ringaskiddy - the commercial drug substance manufacturer. Batch and stability data demonstrate that primary and stability batches are comparable.

The commercial packaging is foil/foil blisters (10 capsules per blister) in cartons (120 capsules per carton). The primary stability batches were packaged in a (b) (4)

(b) (4) were selected for the commercial blisters. These changes are not expected to affect the performance of the blisters.

Up to 30 months of long-term (25 °C/60% RH) stability data are provided. No trending is noted for appearance, assay, and degradants. The total degradants remained at NMT (b) (4)% under all the storage conditions suggesting robust stability of tafamidis meglumine capsules. However, dissolution decreased over time. For capsules stored at 30°C/75%RH, the dissolution fell below the  $Q = \frac{(b)(4)}{(4)}\%$  criterion at the 30-month time point. However, capsules stored at 25°C/60%RH met the acceptance limit through 30-month. Based on the dissolution behavior, the Applicant is proposing only 24-months of shelf-life at controlled room temperature.

Tafamidis meglumine 20 mg immediate release soft gelatin capsule is manufactured by a (b) (4)

available equipment in the pharmaceutical industry. Tafamidis meglumine 20 mg will be provided as a size 9.5 oblong opaque yellow soft gelatin capsule filled with a white to pink colored suspension. The capsule is printed with “VYN 20” in red. No overages are incorporated into the formulation or manufacturing process. Risk associated with (b) (4) is low. Development data confirm that detection of (b) (4) is possible based on the current control strategy. The in-process controls are adequate to ensure consistent manufacturing.

Microbiological acceptance criteria for tafamidis meglumine soft gelatin capsules has been omitted from the specification based on ICH Q6A risk assessment and data collected during clinical, validation and registration batch testing. The formulation does

not contain (b) (4)  
The non-sterile, (b) (4) capsules are manufactured in a GMP-controlled facility with an (b) (4)  
Microbiological quality of the product has been tested in line with (b) (4) (b) (4) preparations for oral use, on the clinical batches and the registration batches manufactured at the commercial site.

The proposed dissolution method [900 mL of 50 mM sodium phosphate buffer pH 6.8 (Tier 1) and 50 mM sodium phosphate buffer pH 6.8 with 1750 activity units of pancreatin per liter (Tier 2) using USP Apparatus 2 (paddle) at 75 rpm] has been demonstrated to be sufficiently discriminating towards the change in the product during the stability testing/storage. Based on the provided information/data, the proposed dissolution method is deemed acceptable for quality control testing of the proposed finished drug product. The proposed dissolution acceptance criterion (not less than (b) (4)% (Q) in 30 minutes) is appropriately selected for quality control testing of the proposed product and therefore is acceptable. In-vitro bridging studies are not needed for the proposed product as the Applicant performed a comparative bioavailability study (Study # B3461044) using the pre-change (manufactured at (b) (4) and the post-change/to-be-marketed products (manufactured at Catalent).

The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The applicant included a use amount that was consistent with the claim. The required statement of no extraordinary circumstances also was provided, in accordance with 21 CFR 25.15. The CDER EA Team reviewed the claim and responded that because the substance is a new molecular entity and has a thyroid-related mechanism of action potentially related to FDA's 2016 guidance on hormonally active drugs (USFDA, 2016), additional information should be provided by the applicant to assist in a determination of no extraordinary circumstances, including regarding cumulative impact. The EA Team reviewed the additional data that was provided and found the data to be indicative of no significant environmental impact from this application. Therefore, the claim for an exclusion from an EA is acceptable.

### C. Special Product Quality Labeling Recommendations (NDA only)

In addition to the current NDA, the applicant also submitted a NDA for tafamidis free acid softgel capsules. Tafamidis is the active moiety in both products. Although bioequivalence of four – 20 mg tafamidis meglumine capsules to one – 61 mg tafamidis free acid capsule was established via the clinical bioequivalence study, the two products are not substitutable as **80 mg of tafamidis meglumine IS NOT equivalent to 61 mg of tafamidis free acid.** As such, labeling should clearly indicate that the two products under the different NDAs should not be substituted.

The review team consulted the Product Quality Labeling Committee (PQL) for guidance on labeling these two products with the same active moiety. The following recommendations from the PQL were communicated to the larger multi-disciplinary team to differentiate these products.

**Established Names**

- For NDA 211996, Tafamidis Meglumine Capsules is the appropriate established name. The salt appears to affect some aspects of ADME.
- For NDA 212161, Tafamidis Capsules is the appropriate established name.

**Proprietary Names and Labeling**

- PQL defers proprietary naming decisions to OSE/DMEPA. While PQL prefers the use of a *proprietary name* of one product and the *same root proprietary name + modifier* for the other product. We think this is a reasonable approach to consider. If agreeable, this approach can also support inclusion of both products within the same PI. Again, we defer to OSE/DMEPA. However, PQL does not object to the applicant’s proposal (Vyndaqel (tafamidis meglumine) Capsules and Vyndamax (tafamidis) Capsules) to keep the same root proprietary name (“Vynda”) with different endings (“*qel*” for tafamidis meglumine capsules, “*max*” for tafamidis free acid capsules).

**Salt Equivalency Statements**

We recognize the potential for confusion between the products is greater considering the prominence of the salt equivalency statement on the principle display panel (b) (4). However, the equivalency statement is required by the FD&C Act and USP <7>. Absence of the equivalency statement may cause the product to be misbranded. To address concerns regarding potential confusion, PQL recommends the following:

- Minimize the prominence of the equivalency statement.
  - Include (b) (4) equivalency statement on the carton labeling side panel and section 11 DESCRIPTION. (b) (4)
  - Note the equivalency statement is required on the container panel. However, because this product has blister packs, we are unable to add to the equivalency statement to the container label. (b) (4)

(b) (4)

(b) (4)

- Include a prominent statement to warn against inappropriate substituting/interchanging (e.g. container, carton) on a mg to mg basis between the products. Also include this statement in PI, perhaps section 2 DOSAGE AND ADMINISTRATION.

**D. Final Risk Assessment**

From Initial Risk Identification		Review Assessment		
Critical Quality Attributes	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
<i>Assay</i>	<b>Low</b>		<b>Low</b>	
<i>Physical Stability</i>	<b>Medium</b>	(b) (4)	<b>Low</b>	
<i>Content Uniformity</i>	<b>Medium</b>		<b>Low</b>	
<i>Microbial Limits</i>	<b>Low</b>		<b>Low</b>	
<i>Dissolution</i>	<b>Medium</b>		<b>Low</b>	
<i>Leakage</i>	<b>Low</b>			<b>Low</b>
<i>Moisture Content</i>	<b>Low</b>		<b>Low</b>	
(b) (4)	<b>Medium</b>	(b) (4)	<b>Low</b>	



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**LABELING**

**I. Package Insert**

**1. Highlights of Prescribing Information**

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	VYNDAQEL® (tafamidis meglumine)
Dosage form, route of administration	Capsule, for oral administration
Controlled drug substance symbol (if applicable)	n/a
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Capsules: Tafamidis meglumine 20 mg

**2. Section 2 Dosage and Administration**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	n/a

**3. Section 3 Dosage Forms and Strengths**

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(4))
Available dosage forms	capsule
Strengths: in metric system	20 mg
Active moiety expression of strength with equivalence statement (if applicable)	tafamidis meglumine 20 mg Note: Upon consultation with OPPQ, to minimize dosing error, salt equivalency statement will be provided in section 11 of the PI only.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	yellow, opaque, oblong capsule, printed with "VYN 20" in red.

**4. Section 11 Description**

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	adequate
Dosage form and route of administration	adequate
Active moiety expression of strength with equivalence statement (if applicable)	tafamidis meglumine 20 mg (equivalent to 12.2 mg of tafamidis free acid)
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	adequate
Statement of being sterile (if applicable)	n/a
Pharmacological/ therapeutic class	VYNDAQEL (tafamidis meglumine) is a selective stabilizer of transthyretin.
Chemical name, structural formula, molecular weight	2 (3,5 dichlorophenyl) 1,3 benzoxazole 6 carboxylic acid mono (1 deoxy 1 methylamino D glucitol)  C <sub>14</sub> H <sub>7</sub> Cl <sub>2</sub> NO <sub>3</sub> C <sub>7</sub> H <sub>17</sub> NO <sub>5</sub>  503.33 g/mol
If radioactive, statement of important nuclear characteristics.	n/a
Other important chemical or physical properties (such as pKa or pH)	n/a

**5. Section 16 How Supplied/Storage and Handling**

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	20 mg
Available units (e.g., bottles of 100 tablets)	(b) (4) They are described adequately.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate.
Special handling (e.g., protect from light)	n/a
Storage conditions	Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

**Reviewer’s Assessment of Package Insert: *Adequate***

The prescribing information meets all the regulatory requirements from a CMC perspective.

**II. Labels:**

**1. Container Label**

Shown below is the most recent carton edit submitted by the Applicant (email dated 03-21-2019; eCTD submission pending).

APPEARS THIS WAY ON ORIGINAL

(b) (4)



## ***2. Carton Label***

(b) (4)



Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Vyndaqel (tafamidis meglumine)	Vyndaqel (tafamidis meglumine)
Dosage strength	20 mg	20 mg
Net contents	Not listed – but acceptable for small label.	30 capsules
“Rx only” displayed prominently on the main panel	No – but acceptable for small label.	yes
NDC number (21 CFR 207.35(b)(3)(i))	NDC 0069-1975-12	NDC 0069-1975-40
Lot number and expiration date (21 CFR 201.17)	Adequate	Adequate
Storage conditions	No – but acceptable for small label.	Adequate
Bar code (21CFR 201.25)	Adequate	Adequate
Name of manufacturer/distributor	Adequate	Adequate
And others, if space is available	n/a	n/a

**Reviewer’s Assessment of Labels: *Adequate pending further edits***

The Agency is still negotiating the labeling edits with the Applicant. Tafamidis meglumine and tafamidis are not bioequivalent and hence not substitutable on a mg-to-mg basis of the free acid. To minimize the medication error, the Agency proposed the following statement on the carton label: “Vyndaqel is NOT substitutable on a mg per mg basis with other tafamidis products.” However, the Applicant is proposing the following language instead: (b) (4)  
(b) (4) on a per mg basis.” CMC will work with DMEPA to finalize an acceptable statement.

**List of Deficiencies:** None

**Overall Assessment and Recommendation:** *Adequate*

**Primary Labeling Reviewer Name:** *Mariappan Chelliah*

**Secondary Reviewer Name:** *Wendy Wilson-Lee*



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## BIOPHARMACEUTICS

### PRODUCT BACKGROUND

**NDA:** 211996; 505(b)(1)

**Drug Product Name / Strength:** Tafamidis Meglumine Capsules/20 mg

**Route of Administration:** Oral

**Indication:** Transthyretin related familial amyloid cardiomyopathy

**Submission Date:** 08/30/2018 (Original)

**Applicant Name:** FoldRx, a wholly owned subsidiary of Pfizer, Inc.

### BACKGROUND

The proposed drug product, Tafamidis Meglumine Capsules/20 mg, is a soft gelatin capsules developed for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) due to wild type or variant transthyretin to slow progression of cardiomyopathy and to reduce the combination of mortality and cardiovascular hospitalization.

The submission of this 505 (b)(1) NDA is supported by a pivotal efficacy and safety trial (B3461028). The Biopharmaceutics review is focused on the evaluation of (1) the proposed dissolution method and acceptance criteria, and (2) formulation bridging, as presented below.

### REVIEW SUMMARY

**Dissolution Method:** The proposed product is an immediate-release soft-gelatin capsule filled with a suspension that contains 20 mg of tafamidis meglumine. The proposed dissolution method [900 mL of 50 mM sodium phosphate buffer pH 6.8 (Tier 1) and 50 mM sodium phosphate buffer pH 6.8 with 1750 activity units of pancreatin per liter (Tier 2) using USP Apparatus 2 (paddle) at 75 rpm] has been demonstrated to be sufficiently discriminating towards the change in the product during the stability testing/storage. Based on the provided information/data, the proposed dissolution method is deemed acceptable for quality control of the proposed finished drug product.

**Dissolution Acceptance Criteria:** The Applicant's proposed dissolution acceptance criterion (not less than  $\frac{(b)}{(4)}\%$  (Q) in 30 minutes) is appropriately selected for quality control testing of the proposed product and therefore is acceptable.

**Formulation Bridging:** In-vitro bridging studies are not needed for the proposed product as the Applicant performed a comparative bioavailability study (Study # B3461044) using the pre-change (manufactured at  $\frac{(b)}{(4)}$ ) and the post-change/to-be-marketed products (manufactured at Catalent). The

bioavailability study results to support the proposed bridging will be evaluated by the Office of Clinical Pharmacology.

**Conclusion and Recommendation:** From the Biopharmaceutics perspective, NDA 211996 for Tafamidis Meglumine Capsules/20 mg, is recommended for **APPROVAL**.

The approved dissolution method and acceptance criteria for the quality control of the finished immediate release drug product at batch release and during stability testing are:

<b>FDA's Approved Dissolution Method and Acceptance Criteria for Tafamidis Meglumine Capsules/20 mg</b>	
Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	75 rpm
Volume	900 mL
Medium	Tier 1: 50 mM sodium phosphate buffer pH 6.8 Tier 2: 50 mM sodium phosphate buffer pH 6.8 with 1750 activity units of pancreatin per liter
Temperature	37.0 ± 0.5°C
Acceptance Criterion	NLT <sup>(b)</sup> <sub>(4)</sub> % (Q) in 30 minutes

***Primary Biopharmaceutics Reviewer Name***

**Kaushalkumar Dave, Ph.D.**

Division of Biopharmaceutics, ONDP, OPQ

***Secondary Reviewer Name***

I concur with Dr. Dave's Biopharmaceutics assessment and recommendation.

**Jing Li, Ph.D.**

Division of Biopharmaceutics, ONDP, OPQ



## BIOPHARMACEUTICS ASSESSMENT

### 1. LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	Received date	Document
0001	08/30/2018	Original NDA Submission
0012	12/27/2018	Quality/Response to Information Request

### 2. DRUG PRODUCT

The proposed product is an immediate-release soft-gelatin capsule filled with a suspension that contains 20 mg of tafamidis meglumine. The suspension is composed of a tafamidis meglumine drug substance suspended (b) (4). The composition of the proposed capsules (b) (4) is provided in *Appendix 1*. (b) (4)

The proposed product, Tafamidis Meglumine Soft Gelatin Capsules, 20 mg, was developed by (b) (4) and later purchased by Pfizer who transferred the manufacturing of the proposed product from (b) (4) Catalent. While the qualitative and quantitative composition of the active fill suspension used at both (b) (4) Catalent is identical, there are changes in terms of the (b) (4). The Applicant performed a comparative bioavailability study (Study # B3461044) using the pre-change (manufactured at (b) (4) and the post-change/to-be-marketed products (manufactured at Catalent). The bioavailability study results will be evaluated by the Office of Clinical Pharmacology.

<sup>1</sup>[https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80282622&\\_afRedirect=2737207974128522](https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80282622&_afRedirect=2737207974128522)

### 3. BCS DESIGNATION: *NOT APPLICABLE*

#### **Solubility**

The Applicant studied the solubility of tafamidis meglumine in the physiological pH range. The results of the experimental solubility summarized in Table 1 indicate that tafamidis meglumine is a poorly soluble drug substance, per the BCS criteria, and exhibits pH independent solubility/insolubility in the pH range of (b) (4) and increased solubility at a higher pH (i.e. water and pH 6.8 buffer).

**Table 1:** Aqueous Solubility of tafamidis meglumine

<b>Solution</b>	<b>Solubility (mg/mL)</b>
Water	> 4.628
0.1 N NaOH	> 4.187
Buffer, pH 6.8	3.121
Buffer, pH 5.0	0.000
Buffer, pH 4.5	0.000
Buffer, pH 3.0	0.007
0.1 N HCl	0.000

#### **Permeability**

No information of permeability of the drug substance was provided for this application. However, the Applicant stated that a study (#B3461017) was conducted to investigate the absorption, metabolism and excretion of <sup>14</sup>C-tafamidis meglumine in healthy male subjects following a single dose of 20 mg tafamidis meglumine containing 50 µCi <sup>14</sup>C-tafamidis meglumine. The results indicated that the mean total recovery of radioactivity (both urine and feces combined) was 80.85% of the total administered dose.

The Applicant stated that based on the aqueous solubility and permeability data above, tafamidis is categorized as a BCS Class IV compound (low solubility and low permeability).

It is important to note that no BCS designation request has been submitted by the Applicant and no designation has been determined by the FDA for tafamidis meglumine.

### 4. DISSOLUTION INFORMATION

#### **Selection of the dissolution method**

For quality control testing of the proposed product, the Applicant selected the following dissolution method.

**Table 2:** Proposed Dissolution Method and Acceptance Criteria for Tafamidis Meglumine Capsules/20 mg

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	75 rpm
Volume	900 mL
Medium	Tier 1: 50 mM sodium phosphate buffer pH 6.8 Tier 2: 50 mM sodium phosphate buffer pH 6.8 with 1750 activity units of pancreatin per liter
Temperature	37.0 ± 0.5°C
Acceptance Criteria	Not less than (NLT) <sup>(b)</sup> <sub>(4)</sub> % (Q) in 30 minutes



(b) (4)

<sup>2</sup>[https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80282622&\\_afRedirect=2737207974128522](https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80282622&_afRedirect=2737207974128522)

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based on the fresh batch data and the pharmacokinetic properties of the drug. The clinical data for the proposed product show that it has a median T<sub>max</sub> value of 2 hours. The Applicant has proposed the dissolution acceptance criterion of 'Not less than (NLT) (b) (4)% (Q) in 30 minutes' (b) (4). The proposed dissolution acceptance criterion is adequately selected and therefore is **acceptable** for quality control testing of the proposed product.

## 5. FORMULATION BRIDGING

The proposed product, Tafamidis Meglumine Soft Gelatin Capsules, 20 mg, was developed by (b) (4) and later purchased by Pfizer who transferred the manufacturing of the proposed product from (b) (4) Catalent. While the qualitative and quantitative composition of the active fill suspension used at both (b) (4) Catalent is identical, there are changes in terms of the (b) (4). The Applicant performed a comparative bioavailability study (Study # B3461044) using the pre-change (manufactured at (b) (4) and the post-change/to-be-marketed products (manufactured at Catalent). The bioavailability study results to support the proposed bridging will be evaluated by the Office of Clinical Pharmacology.

## 6. BIOWAIVER REQUEST

Only one strength (20 mg capsules) is proposed under the current NDA and therefore no biowaiver request is submitted or is necessary.

## 7. LIST OF DEFICIENCIES

None

## Appendix 1

**Table:** Composition of Tafamidis Meglumine Capsules, 20 mg

Name of Ingredient	Function	Reference to Standard	Unit formula	
			mg/capsule	%
(b) (4)				
Tafamidis Meglumine	Drug Substance	Pfizer	20.0 <sup>1</sup>	(b) (4)
Polyethylene Glycol 400	(b) (4)	Ph. Eur./NF/JP		(b) (4)
Polysorbate 80		Ph. Eur./NF/JP		
Sorbitan Monooleate		Ph. Eur./NF/JPE		
(b) (4)				
Gelatin	(b) (4)	(b) (4)		(b) (4)
Sorbitol				
(b) (4)				
Iron Oxide, Yellow				
Titanium Dioxide				
Purified Water <sup>4</sup>	USP, Ph. Eur./JP		(b) (4)	

N/A = Not Applicable

<sup>1</sup> Tafamidis meglumine 20 mg is equivalent to 12.2 mg active of tafamidis as the free acid

(b) (4)



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Dave

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Li

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**Recommendation:** **APPROVAL**

**NDA 212161  
Review #01**

Drug Name/Dosage Form	Tafamidis Capsules
Strength	61 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	FoldRx a wholly owned subsidiary of Pfizer, Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
<i>Original (SD 1)</i>	02-NOV-2018	<i>Amendment (SD 7)</i>	15-FEB-2019
<i>Amendment (SD 3)</i>	11-DEC-2018	<i>Amendment (SD 8)</i>	11-MAR-2019
<i>Amendment (SD 4)</i>	27-DEC-2018	<i>Amendment (SD 10)</i>	28-MAR-2019
<i>Amendment (SD 5)</i>	28-JAN-2019		

**Quality Review Team**

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Charles Jewell		ONDP
Drug Product	Mariappan Chelliah	Wendy Wilson-Lee	
Labeling			
Environmental	James Laurenson		
Manufacturing	Frank Wackes	Ying Zhang	OPF
Biopharmaceutics	Kaushalkumar Dave	Jing Li	ONDP
Regulatory Business Process Manager	Grafton Adams		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

## Quality Review Data Sheet

**1. RELATED/SUPPORTING DOCUMENTS**

**A. DMFs:**

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	Catalent Pharma Solutions LLC	(b) (4)	Adequate	29-MAR-2019	

**B. Other Documents: *IND, RLD, or sister applications***

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	71880	Tafamidis meglumine for treatment of TTR familial amyloid cardiomyopathy
IND	74866	Tafamidis meglumine for treatment of TTR familial amyloid polyneuropathy
NDA	202737	Tafamidis meglumine capsules for treatment of transthyretin amyloidosis in adult patients with symptomatic polyneuropathy
NDA	211996	Tafamidis meglumine capsules for treatment of TTR amyloid cardiomyopathy

**2. CONSULTS**

None.

## Executive Summary

### I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of Tafamidis Capsules, 61 mg.

### II. Summary of Quality Assessments

#### A. Product Overview

FoldRx seeks approval of tafamidis free acid soft gelatin capsules under NDA 212161 for the reduction of (b) (4) cardiovascular-related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) under the 505(b)(1) pathway. ATTR-CM is a rare and fatal disorder. There are no FDA-approved treatments for ATTR-CM. FDA granted orphan designation for a slightly different indication in February 2017. FDA granted fast track designation in May 2017 and breakthrough therapy designation in May 2018. A sister NDA was also submitted and granted priority review for a tafamidis meglumine soft gelation capsule product (NDA 211996).

The drug product is a soft gelatin capsule containing 61 mg tafamidis free acid, formulated as a suspension in (b) (4)

(b) (4) The proposed dose recommendation is 61 mg daily. The Applicant contends that the (b) (4)

(b) (4)

(b) (4) The drug product control strategy includes in-process controls for (b) (4)

(b) (4)

(b) (4) FoldRx indicates in the submission that all other quality attributes and process parameters identified as non-critical are controlled through the Pfizer and Catalent quality systems. This approach will require an in-depth evaluation during the review.

The initial risk assessment identified content uniformity, (b) (4) physical stability and dissolution as moderate risks. The drug product contains a low drug substance load. The drug substance's low solubility (b) (4)

(b) (4)

<b>Proposed Indication(s) including Intended Patient Population</b>	<i>for the reduction of (b) (4) cardiovascular-related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy</i>
<b>Duration of Treatment</b>	<i>Chronic</i>
<b>Maximum Daily Dose</b>	<i>61 mg</i>
<b>Alternative Methods of Administration</b>	<i>None</i>

**B. Quality Assessment Overview**

Tafamidis (in the free acid form) is proposed for manufacture for commercial use at the Pfizer Ringaskiddy Site (Ireland) using the process known as Process C2, optimized for commercial use. Material manufactured by this process was used in most of the clinical studies for the drug product manufactured from Tafamidis. There is a version of the manufacturing process (b) (4)

(b) (4)

(b) (4) A single stable polymorph (Form 1) is consistently produced using the commercial manufacturing process, this material is demonstrated to be stable. Other less stable polymorphs (b) (4) are known but not produced in the current process (b) (4). This supports manufacturability of the drug product.

The impurity profiles of the designated starting materials (commercially available substances) have been demonstrated to be adequately understood, with respect to origin of impurities. Process impurities, and purge of all impurities is understood. No impurities are specified above (b) (4) % in the release specification, and all unspecified impurities are limited to below (b) (4) %. An appropriate mutagenic impurity risk assessment was done. Two identified mutagenic impurities were observed to be controlled to below (b) (4) % the threshold of toxicological concern (TTC, described in ICH M7) and thus are not tracked as part of release specification attributes. Justification for this is adequate.

Adequate stability studies demonstrate stability for at least (b) (4) months when stored as recommended by the applicant. No degradation is observed under (b) (4). The drug substance is demonstrated not sensitive to light. A retest period of (b) (4) months is designated for this drug substance by the FDA (concurrence with the applicant's request).

Tafamidis 61 mg will be provided as size 9.5 soft gelatin capsules. It is formulated as drug substance suspended in (b) (4)

(b) (4) The capsules are manufactured by (b) (4) and the CMC information for the soft gelatin capsule shell is cross-referenced to (b) (4) DMF (b) (4). The controls for all the excipients are adequate and the excipients are qualified.

The proposed specification is adequate to control the quality of the drug product. The controls for impurities meet ICH Q3B(R2). The Applicant has adequately validated all the non-compendial analytical methods used in the drug product testing. Drug substance for the primary stability batches were supplied by Pfizer Ringaskiddy, the proposed commercial drug substance manufacturer. All the primary stability batches met the drug product specification.

The commercial batches will be packaged in foil/foil blisters (10 capsules per blister) and then in cartons (30 capsules per carton). The primary stability batches were packaged in a

(b) (4)  
(b) (4)  
(b) (4) These changes should not affect the performance of the blisters.

Up to 12 months of long-term (25 °C/60% RH) stability data are provided. Other than small increase in capsule fill moisture content, the drug product does not show any trending. The statistical evaluation supports extending the shelf-life from 12 months to 24 months. The proposed shelf-life of 24 months is acceptable. The proposed storage condition is controlled room temperature.

Tafamidis meglumine 61 mg immediate release soft gelatin capsule is manufactured by a (b) (4)

The capsule is in-line printed with "VYN 61" in white ink on the opaque reddish-brown soft capsule. No overages are incorporated into the formulation or manufacturing process for the tafamidis meglumine 61 mg immediate release soft gelatin capsule manufactured at Catalent. No scale up is proposed from registration batch to the commercial batch

Microbiological quality of the product has been tested in line with (b) (4) (b) (4) preparations for oral use, on the clinical batches and the registration batches manufactured at the commercial site. All three packaged stability batches were assessed for total aerobic count, total molds and yeast count at time zero. Microbiological quality was established at the initial time point and was verified at 12 months on the 30°C/75%RH stability sample. The formulation does not contain (b) (4)

(b) (4) Adequate environmental controls coupled with testing of each lot of incoming raw materials ensure microbiological quality of the product.

The Biopharmaceutics review focused on the evaluation of (1) the proposed dissolution method and acceptance criteria, and (2) formulation bridging, as presented below. The proposed product is an immediate-release soft-gelatin capsule containing 61 mg of (b) (4) tafamidis filled as a suspension. The selection of the proposed dissolution study conditions [900 mL of 0.05M sodium phosphate buffer pH 6.8 with 1% Tween® 80 (Tier 1) and 0.05M sodium phosphate buffer pH 6.8 with 1% Tween® 80 with NMT 2000 units of protease activity/L (Tier 2) using USP Apparatus 2 (paddle) at 75 rpm] is adequately justified and supported by the data. The provided dissolution data demonstrate that the proposed dissolution method is discriminating towards the drug substance particle size and certain formulation variables. Based on the provided information/data, the proposed dissolution method is deemed acceptable for quality control of the proposed drug product.

The applicant's proposed dissolution acceptance criterion (not less than (b) (4)% (Q) in 30 minutes) is appropriately selected for quality control testing of the proposed product and therefore is acceptable. In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The applicant included a use amount that was consistent with the claim. The required statement of no extraordinary circumstances also was provided, in accordance with 21 CFR 25.15. The CDER EA Team reviewed the claim and responded that because the substance is a new molecular entity and has a thyroid-related mechanism of action potentially related to FDA's 2016 guidance on hormonally active drugs (USFDA, 2016), additional information should be provided by the applicant to assist in a determination of no extraordinary circumstances, including regarding cumulative impact. The EA Team reviewed the additional data that was provided and found the data to be indicative of no significant environmental impact from this application. Therefore, the claim for an exclusion from an EA is acceptable.

### C. Special Product Quality Labeling Recommendations (NDA only)

In addition to the current NDA, the applicant also submitted a NDA for tafamidis meglumine softgel capsules. Tafamidis is the active moiety in both products. Although bioequivalence of four – 20 mg tafamidis meglumine capsules to one- 61 mg tafamidis free acid capsule was established via the clinical bioequivalence study, the two products are not substitutable as **80 mg of tafamidis meglumine IS NOT equivalent to 61 mg of tafamidis free acid.** As such, labeling should clearly indicate that the two products under the different NDAs should not be substituted.

The review team consulted the Product Quality Labeling Committee (PQL) for guidance on labeling these two products with the same active moiety. The following recommendations from the PQL were communicated to the larger multi-disciplinary team to differentiate these products.

#### **Established Names**

- For NDA 211996, Tafamidis Meglumine Capsules is the appropriate established name. The salt appears to affect some aspects of ADME.
- For NDA 212161, Tafamidis Capsules is the appropriate established name.

#### **Proprietary Names and Labeling**

- PQL defers proprietary naming decisions to OSE/DMEPA. While PQL prefers the use of a *proprietary name* of one product and the *same root proprietary name + modifier* for the other product. We think this is a reasonable approach to consider. If agreeable, this approach can also support inclusion of both products within the same PI. Again, we defer to OSE/DMEPA. However, PQL does not object to the applicant's proposal (Vyndaqel (tafamidis meglumine) Capsules and Vyndamax (tafamidis) Capsules) to keep the same root proprietary name ("Vynda") with different endings ("*qel*" for tafamidis meglumine capsules, "*max*" for tafamidis free acid capsules).
- Include a prominent statement to warn against inappropriate substituting/interchanging (e.g. container, carton) on a mg to mg basis between the products. Also include this statement in PI, perhaps section 2 DOSAGE AND ADMINISTRATION.

#### **D. Final Risk Assessment**

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From Initial Risk Identification		Review Assessment		
Critical Quality Attributes	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
<i>Assay</i>	Low		Low	
<i>Physical Stability</i>	Medium	(b) (4)	Low	
<i>Content Uniformity</i>	Medium		Low	
<i>Microbial Limits</i>	Low		Low	
<i>Dissolution</i>	Medium		Low	
<i>Leakage</i>	Low		Low	
<i>Moisture Content</i>	Low		Low	
(b) (4)	Medium	(b) (4)	Low	



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**LABELING**

**I. Package Insert**

**1. Highlights of Prescribing Information**

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	TRADENAME (tafamidis)
Dosage form, route of administration	adequate
Controlled drug substance symbol (if applicable)	n/a
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	adequate

**2. Section 2 Dosage and Administration**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	n/a

**3. Section 3 Dosage Forms and Strengths**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Capsule
Strengths: in metric system	61 mg
Active moiety expression of strength with equivalence statement (if applicable)	n/a
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	reddish brown, opaque, oblong capsule, printed with "VYN 61" in white.

**4. Section 11 Description**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	adequate
Dosage form and route of administration	adequate
Active moiety expression of strength with equivalence statement (if applicable)	n/a
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	adequate
Statement of being sterile (if applicable)	n/a
Pharmacological/ therapeutic class	adequate
Chemical name, structural formula, molecular weight	adequate
If radioactive, statement of important nuclear characteristics.	n/a
Other important chemical or physical properties (such as pKa or pH)	n/a

**5. Section 16 How Supplied/Storage and Handling**

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Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Adequate
Available units (e.g., bottles of 100 tablets)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate
Special handling (e.g., protect from light)	n/a
Storage conditions	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

**Reviewer’s Assessment of Package Insert: *Adequate***

The prescribing information meets regulatory requirements from a CMC perspective. Note that DMEPA recently accepted VYNDAMAX as the tradename. Accordingly, TRADENAME will be replaced with VYNDAMAX everywhere in the labeling.

**II. Labels:**

**1. *Container and Carton Labels***

Shown below is the most recent carton edit submitted by the Applicant (email dated 03-21-2019; eCTD submission pending).

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## **2. Carton Label**

Shown below is the most recent carton (30 ct box) edit submitted by the Applicant (email dated 03-21-2019; eCTD submission pending).

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(b) (4)



Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	TRADENAME (tafamidis)	TRADENAME (tafamidis)
Dosage strength	61 mg	61 mg
Net contents	Missing – but acceptable for small labels.	30 capsules
“Rx only” displayed prominently on the main panel	Missing – but acceptable for small labels.	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	NDC 0069-8730-01	NDC 0069-8730-30
Lot number and expiration date (21 CFR 201.17)	Adequate	Adequate
Storage conditions	Missing – but acceptable for small labels.	Adequate
Bar code (21CFR 201.25)	Adequate	Adequate
Name of manufacturer/distributor	Adequate	Adequate
And others, if space is available	n/a	n/a

**Reviewer’s Assessment of Labels: *Adequate pending further edits***

The Agency is still in the process of negotiating the labeling edits with the Applicant. Tafamidis meglumine and tafamidis are not bioequivalent, and hence not substitutable, on a mg-to-mg basis of the free acid. The Agency proposed the following statement on the carton label: “TRADENAME is NOT substitutable on a mg per mg basis with other tafamidis meglumine products.” (b) (4) the Applicant is proposing the following language instead: (b) (4) (b) (4) on a per mg basis.” CMC will work with DMEPA to finalize an acceptable statement.

***List of Deficiencies: None***

***Overall Assessment and Recommendation: Adequate***

***Primary Labeling Reviewer: Mariappan Chelliah***

***Secondary Reviewer: Wendy Wilson-Lee***



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## BIOPHARMACEUTICS

### PRODUCT BACKGROUND

**NDA:** 212161; 505(b)(1)

**Drug Product Name / Strength:** Tafamidis Capsules/61 mg

**Route of Administration:** Oral

**Indication:** Transthyretin related familial amyloid cardiomyopathy

**Submission Date:** 08/30/2018 (Original)

**Applicant Name:** FoldRx, a wholly owned subsidiary of Pfizer, Inc.

### BACKGROUND

The proposed product, Tafamidis Soft Gelatin Capsules, 61 mg, is a 'convenience dosage form' developed as an equivalent of four Tafamidis Meglumine Soft Gelatin Capsules, 20 mg (submitted under NDA 211996) for the treatment of transthyretin amyloidosis (ATTR) in adult patients with cardiomyopathy (due to wild type or variant TTR) to reduce (b) (4) cardiovascular-related hospitalization (ATTR-CM). NDA 211996 is also a 505 (b)(1) submission under review and it is supported by a pivotal efficacy and safety trial (B3461028). (b) (4)

(b) (4) the Applicant developed the proposed product using the free acid form of tafamidis.

The submission of this 505 (b)(1) NDA is supported by a bioavailability Study (# B3461056, a multiple dose pivotal steady-state bioequivalence study in fasted healthy volunteers) of the proposed Tafamidis Soft Gelatin Capsules, 61 mg, relative to 4 x 20 mg Tafamidis Meglumine Capsules (subject of NDA 211996). The current Biopharmaceutics review is focused on the evaluation of (1) the proposed dissolution method and acceptance criteria, and (2) formulation bridging, as presented below.

### REVIEW SUMMARY

**Dissolution Method:** The proposed product is an immediate-release soft-gelatin capsule containing 61 mg of (b) (4) tafamidis filled as a suspension. The selection of the proposed dissolution study conditions [900 mL of 0.05M sodium phosphate buffer pH 6.8 with 1% Tween<sup>®</sup> 80 (Tier 1) and 0.05M sodium phosphate buffer pH 6.8 with 1% Tween<sup>®</sup> 80 with NMT 2000 units of protease activity /L (Tier 2) using USP Apparatus 2 (paddle) at 75 rpm] is adequately justified and supported by the data. The provided dissolution data demonstrate that the proposed dissolution method is discriminating towards the drug substance particle size and certain formulation variables. Based on the provided



**QUALITY ASSESSMENT**  
**Chapter VII -Biopharmaceutics**



information/data, the proposed dissolution method is deemed acceptable for quality control of the proposed drug product.

**Dissolution Acceptance Criteria:** The Applicant’s proposed dissolution acceptance criterion (not less than <sup>(b)</sup><sub>(4)</sub>% (Q) in 30 minutes) is appropriately selected for quality control testing of the proposed product and therefore is acceptable.

**Formulation Bridging:** In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

**Conclusion and Recommendation:** From the Biopharmaceutics perspective, NDA 212161 for Tafamidis Capsules/61 mg, is adequate and recommended for **APPROVAL**.

The approved dissolution method and acceptance criterion for the quality control of the finished immediate release drug product at batch release and during stability testing are:

<b>FDA’s Approved Dissolution Method and Acceptance Criteria for Tafamidis Capsules/61 mg</b>	
Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	75 rpm
Volume	900 mL
Medium	Tier I: 0.05M sodium phosphate NaH <sub>2</sub> PO <sub>4</sub> , pH 6.8 with 1.0% Tween <sup>®</sup> 80; Tier II: 0.05M sodium phosphate NaH <sub>2</sub> PO <sub>4</sub> , pH 6.8 with 1.0% Tween <sup>®</sup> 80 and NMT 2000 units of protease activity /L
Temperature	37.0 ± 0.5°C
Acceptance Criterion	NLT 80% (Q) in 30 minutes

***Primary Biopharmaceutics Reviewer Name***

**Kaushalkumar Dave, Ph.D.**  
Division of Biopharmaceutics, ONDP, OPQ

I concur with Dr. Dave’s Biopharmaceutics assessment and recommendation.

***Secondary Reviewer Name***

**Jing Li, Ph.D.**  
Division of Biopharmaceutics, ONDP, OPQ



**QUALITY ASSESSMENT**  
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**BIOPHARMACEUTICS ASSESSMENT****1. LIST OF SUBMISSIONS REVIEWED**

Submissions Reviewed		
eCTD sequence #	Received date	Document
0001	08/30/2018	Original NDA Submission
0012	02/15/2019	Quality/Response to Information Request

**2. DRUG PRODUCT**

The proposed product is an immediate-release soft-gelatin capsule filled with a suspension containing 61 mg of tafamidis in (b) (4)

(b) (4)

(b) (4) The composition of the proposed capsules (b) (4) is provided in *Appendix 1*.

The proposed product, Tafamidis Soft Gelatin Capsules, 61 mg, is a 'convenience dosage form' developed as an equivalent of four Tafamidis Meglumine Soft Gelatin Capsules, 20 mg (submitted under NDA 211996). Bioequivalence (at steady state) between the 4 x 20 mg tafamidis meglumine soft gelatin capsules and the 61 mg tafamidis soft gelatin capsule was established in study B3461056, a multiple dose pivotal bioequivalence study in fasted healthy volunteers comparing  $AUC_{tau}$ , and  $C_{max}$  at steady state. The bioequivalence study results will be evaluated by the Office of Clinical Pharmacology.

**3. BCS DESIGNATION: *NOT APPLICABLE***

**Solubility**

The Applicant studied the solubility of tafamidis in the physiological pH range. The results of the experimental solubility study, summarized in Table 1, indicate that tafamidis is a poorly soluble drug substance, per the BCS criteria, and exhibits pH independent solubility/insolubility in the pH range of (b) (4) and increased solubility at a higher pH.

**Table 1:** Aqueous Solubility of tafamidis

Aqueous Solution	pH	Tafamidis Solubility (µg/mL)
Water	7.6	17.5
0.02M Acetate-phosphate buffer	2.6	<2.0
0.02M Acetate-phosphate buffer	5.3	<2.0
0.02M Acetate-phosphate buffer	6.3	2.0
0.02M Acetate-phosphate buffer	7.0	15.8
0.02M Acetate-phosphate buffer	7.8	72.8
0.02M Acetate-phosphate buffer	8.0	140.0

**Permeability**

No information of permeability of the drug substance was provided for this application. However, the Applicant stated that a study (#B3461017) was conducted to investigate the absorption, metabolism and excretion of <sup>14</sup>C-tafamidis meglumine in healthy male subjects following a single dose of 20 mg tafamidis meglumine containing 50 µCi <sup>14</sup>C-tafamidis meglumine. The results indicated that the mean total recovery of radioactivity (both urine and feces combined) was 80.85% of the total administered dose.

The Applicant stated that based on the aqueous solubility and permeability data above, tafamidis is categorized as a BCS Class IV compound (low solubility and low permeability).

It is important to note that no BCS designation request has been submitted by the Applicant and no designation has been determined by the FDA for tafamidis.

**4. DISSOLUTION INFORMATION**

**Selection of the dissolution method**

The Applicant provided the following information/data to support the selection of the proposed dissolution method.

**5. FORMULATION BRIDGING**

In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

**6. BIOWAIVER REQUEST**

Only one strength (61 mg capsules) is proposed under the current NDA and therefore no biowaiver request is submitted or is necessary.

**7. LIST OF DEFICIENCIES**

None

## Appendix 1

**Table:** Composition of Tafamidis Capsules, 61 mg

Name of Ingredient	Function	Reference to Standard	Unit formula	
			mg/capsule	%
(b) (4)				
Tafamidis	Drug Substance	Pfizer	61.0	(b) (4)
Polyethylene Glycol 400	(b) (4)	Ph. Eur./NF		(b) (4)
Polysorbate 20		Ph. Eur./NF		
Povidone (K-value 90)		Ph. Eur./USP		
Butylated Hydroxytoluene		Ph. Eur./NF		
(b) (4)				
Gelatin	(b) (4)	(b) (4) Ph. Eur./NF		(b) (4)
Sorbitol	(b) (4)	NA		
(b) (4)		USP/Ph. Eur.		
Iron Oxide, Red		NF, E172		
Purified Water <sup>3</sup>		USP, Ph. Eur.		
(b) (4)				

N/A = Not Applicable

(b) (4)



Kaushalkumar  
Dave

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Jing  
Li

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Wendy  
Wilson- Lee

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