

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Review Completion Date	May 1, 2019
Subject	Evaluation of Need for a REMS
Established Name	Tafamidis meglumine; Tafamidis
Trade Name	Vyndaqel; Vyndamax
Name of Applicant	FoldRx Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Therapeutic Class	Stabilizer of variant and wild-type ATT
Formulation(s)	Oral Capsule
Dosing Regimen	Tafamidis meglumine 80 mg daily; Tafamidis 61 mg daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis - free acid formulation- hereinafter referred to as tafamidis) is necessary to ensure the benefits outweigh its risks. FoldRx Pharmaceuticals, Inc., a subsidiary of Pfizer Inc. (FoldRx), submitted a New Drug Application (NDA) 211996 for tafamidis meglumine and NDA 212161 for tafamidis with the proposed indication to reduce (b) (4) cardiovascular related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) (b) (4). The potential risks associated with tafamidis meglumine and tafamidis include cataracts, embryo fetal toxicity, and hepatotoxicity. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Cardiovascular and Renal Products (DCRP) agree that a REMS is not needed to ensure the benefits of tafamidis meglumine outweigh its risks. There are no risks associated with this drug that rise to inclusion in the Warning and Precautions section, therefore, there is no Warning and Precaution section in the proposed labeling at this time. After further evaluation of the risks listed above including cataracts and hepatotoxicity, they are not necessary to be included in the labeling. The risk of embryo fetal toxicity and a recommendation to consider pregnancy planning prevention in females of reproductive potential will be found in the specific populations section of the label. In addition, the Applicant will be required to complete a postmarketing requirement observational study in women exposed to tafamidis meglumine and tafamidis during pregnancy to assess the risk of pregnancy complications and adverse effects on the developing fetus and neonate.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) tafamidis meglumine and tafamidis is necessary to ensure the benefits outweigh its risks. FoldRx submitted a New Drug Application (NDA) 211996 for tafamidis meglumine and NDA 212161 for tafamidis with the proposed indication to reduce (b) (4) cardiovascular related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) (b) (4) in adults. This application is under review in the division of Cardiovascular and Renal Products (DCRP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Tafamidis meglumine/tafamidis, a new molecular entity (NME),^a is a selective stabilizer of transthyretin (TTR). The binding of tafamidis meglumine/tafamidis to TTR at the thyroxine binding sites inhibits TTR tetramer dissociation, the rate limiting step in the amyloidogenic process. By stabilizing the tetrameric native state of TTR, tafamidis meglumine increases the activation barrier associated with tetramer dissociation and therefore mimics the tetrameric stabilization effect observed with naturally occurring protective trans-suppressor variants.

The proposed indication is to reduce (b) (4) cardiovascular-related hospitalization in patients with wild type transthyretin (wtATTR) or hereditary transthyretin (hATTR) ATTR-CM (b) (4). The proposed dosage form is a 20 mg (12.2 mg tafamidis meglumine) oral capsule. The proposed dosage is 80 mg (four 20 mg capsules) or 61 mg of the free acid formulation for (b) (4) the ATTR-CM indication taken daily (b) (4). The drug can be administered in an inpatient or outpatient setting. The duration of treatment for ATTR-CM (b) (4) is long-term^b.

Tafamidis meglumine (NDA 211996) was granted orphan drug designation by the Agency on February 17, 2012 and granted breakthrough therapy and fast track designation by the agency on May 17, 2017, and May 18, 2018, respectively. Initially, NDA 202737 for tafamidis meglumine was submitted on February 23, 2011 for the treatment of ATTR-PN. NDA 202737 was issued a complete response (CR) on June 15, 2012 citing deficiencies in efficacy data. Additionally, the CR letter stated that (b) (4)

Tafamidis meglumine was first approved on November 16, 2011 in the European Union (EU) for the treatment of ATTR-PN in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Tafamidis meglumine has since been approved for the treatment of ATTR-PN in 41 countries. Presently, tafamidis (meglumine or free acid) is not approved in any jurisdiction for ATTR-CM.

^a Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211996 and NDA 212161 relevant to this review:

- 02/17/2017: Orphan Drug Designation (ODD) granted for treatment of ATTR-CM
- 05/17/2017: Fast Track Designation granted for treatment of ATTR-CM
- 05/18/2018: Breakthrough Designation granted for treatment of ATTR-CM
- 11/02/2018: NDA 211996 (tafamidis meglumine) and NDA 212161 (tafamidis) submissions for treatment of wild-type or hereditary transthyretin amyloid cardiomyopathy received
-  (b) (4)
- 02/19/2019: A mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tafamidis meglumine.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Amyloidosis is the general term used to refer to extracellular deposition of subunits of a variety of proteins. These deposits may result in a wide range of clinical manifestations depending on their type, location, and amount of deposition¹. Transthyretin amyloidosis is a rare, life-threatening multi-systemic disease caused by mutations in the TTR gene that results in rapidly progressive, debilitating morbidity and high mortality.^c TTR protein, also known as prealbumin, is produced primarily in the liver and is normally a carrier of vitamin A. Mutations in TTR cause abnormal amyloid proteins to accumulate and damage body organs and tissue, most commonly the peripheral nerves and heart, resulting in peripheral neuropathy, autonomic neuropathy, and/or cardiomyopathy. The clinical presentation of cardiomyopathy most commonly manifests as heart failure, characterized by dyspnea and edema. Angina and claudication can be present, along with syncope related to arrhythmia or heart block, due to the accumulation of amyloid proteins in the coronary arteries. Peripheral neuropathy symptoms include painful dysesthesias in the feet and hands, as well as loss of sensation, which could potentially lead to thermal burns involving the feet and hands and to joint injury in the lower limbs. Progressive muscle atrophy and motor weakness leads to impaired ambulation and inability to perform other activities of

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

daily living. Autonomic neuropathy leads to debilitating orthostatic hypotension, severe gastrointestinal symptoms (including early satiety, chronic nausea/vomiting, and both diarrhea and constipation), and bladder dysfunction with recurrent urinary tract infections.

Both hATTR and wtATTR amyloidosis have a male predominance (approximately 3:1 male to female ratio) with diagnosis typically occurring in the seventh decade.² Median survival is 4.7 years following diagnosis, and is reduced to 3.4 years when cardiomyopathy is involved.³ Worldwide, it is estimated that 50,000 individuals are affected by hATTR amyloidosis annually.^{4, d} The exact prevalence of wtATTR is uncertain, however, in one article wtATTR was noted to be found in up to 25% of individuals > 85 years of age.⁵

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Currently, no FDA approved treatment options for ATTR-CM exist. Patients with symptomatic ATTR-CM have treatment plans that include therapy for systolic or diastolic heart failure (HF) including heart transplantation if appropriate conditions are met. The main treatment of HF with ATTR-CM includes fluid optimization by administering loop diuretics and spironolactone. High dose beta blockers are poorly tolerated, and calcium channel blockers and digoxin are contraindicated in amyloid cardiac disease. The safety and efficacy of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) is unknown and may be harmful in patients with cardiac amyloidosis.⁶ Amiodarone is used to help with rate control in the event of atrial fibrillation or a permanent ventricular pacemaker can be used if required. Also, patients may receive anticoagulation therapy if warranted.

Two recent FDA-approved therapies for ATTR-PN are Onpattro® (patisiran) approved 08/2018 and Tegsedi® (inotersen) approved 10/2018. Patisiran is part of a new class of drugs called small interfering ribonucleic acid (siRNA) treatment that binds to the TTR protein and prevents its deformation through the RNA interference. Inotersen is a phosphorothioate antisense oligonucleotide that binds to mutant and wtTTR mRNA. Both therapies reduce the production of TTR protein and the resultant TTR deposits in the tissues. Patisiran has a known risk of infusion related reactions which are addressed by a premedication regimen consisting of corticosteroids, H1 and H2 blockers, and acetaminophen or equivalents to reduce the potential of an infusion related reaction.⁷ Inotersen has risks of thrombocytopenia and bleeding events, glomerulonephritis and renal toxicity, embolic stroke, and hepatic effects. Inotersen was approved with a REMS to ensure the benefits outweigh the serious risks of thrombocytopenia and glomerulonephritis. The goal of the inotersen REMS is to mitigate the risk of serious bleeding with severe thrombocytopenia and the risk of glomerulonephritis associated with inotersen. The inotersen REMS includes the following elements to assure safe use (ETASU): prescriber certification, pharmacy certification, safe-use conditions of patient counseling and enrollment, patient monitoring of platelet counts, renal function, appropriateness of continuing treatment, and a registry.⁸

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

Other treatments available for a small subset of patients with ATTR-CM or ATTR-PN include orthotopic liver transplant (OLT) and TTR tetramer stabilizers. OLT essentially eliminates mutant TTR from the circulation but does not affect the hepatic production of wt TTR, which continues to be made by the transplanted liver. OLT is only effective in slowing the progression of disease in patients with an early age of onset (<50 years of age). Consequently, almost two-thirds of patients with hATTR amyloidosis are not transplant-eligible. Even when OLT is possible, morbidity and mortality are substantial; patients require life-long immunosuppressive medications, with their attendant risks of infection and renal injury.

Diflunisal, an oral nonsteroidal anti-inflammatory drug (NSAID), has been used off-label in hATTR amyloidosis patients with both early and late stage neuropathy. Diflunisal has been shown to stabilize transthyretin tetramers, thus preventing release of the amyloidogenic protein subunits.⁹ A phase I study demonstrated that diflunisal 250 mg twice daily successfully complexes to the thyroxine binding site and kinetically stabilizes circulating TTR tetramers, inhibiting release of the TTR monomer required for amyloidogenesis.¹⁰ Based on the Phase I study, a Phase 3 placebo controlled trial was conducted comparing diflunisal 250mg twice daily to placebo for 2 years resulting in a reduced rate of progression in neurologic impairment and preserved quality of life.¹¹

Palliative and symptomatic therapies directed at specific symptoms such as pain, nausea, vomiting, and diarrhea have been the mainstay of treatment despite their limited effectiveness. Most patients continue to experience significant morbidity and mortality associated with disease progression due to the unmet medical need for effective therapies.

4 Benefit Assessment

4.1 ATTR-CM

The pivotal clinical trial (Study B3461028, NCT 01994889) supporting the application is a Phase 3, multicenter, international, double-blind, randomized, 3-arm placebo-controlled study in 441 adults with confirmed ATTR-CM due to variant or wild-type TTR. Patients were randomized 2:1:2 to receive either placebo (n=177), tafamidis meglumine 20 mg (n=88), or tafamidis meglumine 80 mg (n=176) once daily, in addition to standard of care for 30 months. The primary efficacy endpoints were all-cause mortality and frequency of cardiovascular-related hospitalizations. The secondary endpoints of functional capacity and health status were measured by the mean change from baseline to Month-30 using the 6-Minute Walk Test (6MWT) and the Kansas City Cardiomyopathy Questionnaire Overall Summary^e (KCCQ-OS) score, respectively.

Patients who completed the 30-month treatment period were given the option rollover into an ongoing Phase 3 extension study (Study B3461045, NCT02791230) for up to 60 months or until tafamidis

^e The KCCQ-OS score is composed of four domains including Total Symptom (Symptom Frequency and Symptom Burden), Physical Limitation, Quality of Life, and Social Limitation. Domain scores range from 0-100 with higher scores representing better health status.

meglumine for ATTR-CM is approved and available by prescription. During the extension study, patients on active treatment during the parent study continued on their same dose. Placebo patients from the parent study (B3461028) were randomized to either a 20 mg or 80 mg dose of tafamidis meglumine.

The Finkelstein-Schoenfeld (F-S) analysis demonstrated a significant reduction in all-cause mortality and frequency of cardiovascular-related hospitalizations in the pooled tafamidis meglumine 20 mg and 80 mg dose group versus placebo as outlined in Table 1.

Table 1: Primary Analysis Using Finkelstein-Schoenfeld (F-S) Method of All-Cause Mortality and Frequency of Cardiovascular-Related Hospitalizations

Primary Analysis	Pooled Tafamidis meglumine (20 mg + 80 mg) N=264	Placebo N=177
Number (%) Subjects Alive at Month 30	186 (70.5%)	101 (57.1%)
Average Cardiovascular-related Hospitalization During 30-Months (per patient per year) Among those alive at Month 30	0.297	0.455
p-Value from F-S Method	0.0006	

Additionally, the analysis of the individual components, all-cause mortality and cardiovascular related hospitalization, demonstrated significant reductions for tafamidis meglumine versus placebo. The hazard ratio from the all-cause mortality Cox proportional hazard model for pooled tafamidis meglumine was 0.70 (95% CI 0.51, 0.96), indicating a 30% reduction in the risk of death relative to the placebo group (p=0.026). There were significantly fewer cardiovascular related hospitalizations with pooled tafamidis meglumine 138 out of 264 (52.3%) compared with placebo 107 out of 177 (60.5%) with a reduction in risk of 32% (RR = 0.68, 95% CI 0.5639, 0.8107, p<0.0001).

The two secondary endpoints, functional capacity and health status as measured by the 6MWT and KCCQ-OS, demonstrated a statistically significant and clinically meaningful difference. A significant treatment effect favoring tafamidis meglumine for functional capacity and health status was first observed at Month 6 and remained consistent through Month 30 for both 6MWT distance and KCCQ-OS. At month 30, the 6MWT demonstrated a statistically significant difference in the pooled tafamidis meglumine group by 75.7 meters (CI 57.6, 93.8) in comparison to the placebo arm. The KCCQ-OS demonstrated a statistically significant difference in the pooled tafamidis meglumine group of 13.7 (CI 9.5, 17.8) points in comparison to the placebo group.

(b) (4)

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5 Risk Assessment & Safe-Use Conditions

The safety population is comprised 377 ATTR-CM patients in Phase 3 study (B3461028) with a mean exposure duration of 24.5 months. The safety information is also included from 137 ATTR-PN patients in Phase 2 clinical trial (B3461020), with a mean exposure of 44.2 months.

Common Adverse Events:

The most commonly reported adverse events (AEs) >15%, all-causality for ATTR-CM patients treated with tafamidis meglumine (pooled tafamidis meglumine 20 mg + 80 mg) were cardiac failure (28.8%), fall (26.5%), atrial fibrillation (18.9%), dyspnea (18.9%), peripheral edema (17.8%), fatigue (17.0%), dizziness (15.9%), and constipation (15.2%). Asthenia and pneumonia were reported in a higher proportion of patient in both tafamidis meglumine groups compared to placebo.

The most commonly reported in the ATTR-PN patients were diarrhea (28%), UTI (23%), upper abdominal pain (12%), and vaginal infection (12%).

Deaths

72 deaths occurred among the pooled tafamidis meglumine groups and 73 deaths occurred in patients on placebo. Per the clinical reviewer, none of the deaths were assessed as treatment related. Death rates were lower for tafamidis-treated subjects from the ongoing trial and the long-term follow-up cohorts than placebo.

5.1 ADVERSE EVENTS OF SPECIAL INTEREST

5.1.1 Cataracts

DCRP identified a possible safety signal for cataracts noting a higher incidence of these adverse events in both tafamidis meglumine groups compared to the placebo group in the pivotal trial. The exposure adjusted incidence rates for lens disorder across all treatment groups with exposure adjusted IR (95% CI) were 1.83 (0.67, 3.98) for placebo, 3.96 (1.59, 8.16) for tafamidis 20 mg, 5.27 (3.13, 8.34) for tafamidis meglumine 80 mg, and 4.83 (3.12, 7.13) among the pooled tafamidis meglumine group.¹³ DCRP consulted Division of Transplant and Ophthalmology Products to further assess if this signal could be drug-related considering the event rate, time-course, and patient population. The ophthalmology reviewer concluded that 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 AEs including cataract development is not believed to be a signal of a drug-related adverse event.¹⁴

5.1.2 Embryo-Fetal Toxicity

Based on animal studies, tafamidis meglumine has shown developmental toxicity and may cause fetal harm when administered to a pregnant womanⁱ. Limited available human data with tafamidis

ⁱ Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

meglumine use in pregnant women have not identified any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes at a dose of 20 mg/day. There are no available human data with tafamidis meglumine 80 mg. The Division of Pediatric and Maternal Health (DMPH) reviewer, DCRP nonclinical reviewer, and the clinical reviewer agree that the limited available human pregnancy data do not support the animal findings but are insufficient to exclude a potential risk to the fetus and therefore included a "may cause fetal harm" statement in subsection 8.1 of the labeling.¹⁵ Pregnancy planning and prevention should be considered for females of reproductive potential. Furthermore, patients are to be advised that breastfeeding is not recommended during treatment with tafamidis meglumine.

5.1.3 Hepatic Effects

Nonclinical data suggest that the liver may be a target organ for toxicity. As the mechanism of action for tafamidis meglumine involves binding to the thyroxine binding site on TTR found in the liver, liver function was further evaluated. The exposure adjusted incidence rates for hepatotoxicity across all treatment groups with exposure adjusted IR (95% CI) were 13.08 (9.30, 17.89) for placebo, 14.37 (9.11, 21.57) for tafamidis meglumine 20 mg, 12.10 (8.56, 16.61) for tafamidis 80 mg, and 12.87 (9.84, 16.53) among pooled tafamidis meglumine groups, respectively. The Sponsor noted that based on the mechanism of action, there could be a signal. The safety reviewer noted that the AE findings are consistent with laboratory results which indicate some signals for tafamidis meglumine -associated liver enzyme elevations. Despite these laboratory changes, there is no corresponding clinical evidence of hepatotoxicity in the ATTR-CM and ATTR-PN development program. One possible hepatic event associated with tafamidis meglumine was identified, however, the causal association could not be concluded based on the available data thus far. In addition, the two potential Hy's law cases based on liver chemistries in the tafamidis meglumine 80 mg group were determined to be inconsistent with drug induced liver injury per the Agency's safety review team. The elevated liver function tests in these cases were likely secondary to patient's cardiac disease and medical conditions. Also, AE data did not support the risk of hepatotoxicity in patients with ATTR-CM. The safety reviewer finds that hepatotoxicity remains a potential risk for tafamidis meglumine and recommends evaluating potential hepatic events occurring in the post-marketing setting, however at this time will not be included in the labeling.

6 Expected Postmarket Use

The small size of the patient population will likely limit the prescribing of tafamidis meglumine to cardiologists for ATTR-CM (b) (4). This medication will likely be started and continued on an outpatient basis, however since it is ongoing therapy may also be continued on an inpatient basis if needed as it is administered orally. These specialists should be aware to address the potential risk of embryo-fetal toxicity as there are multiple other drugs within their typical prescribing purview which also carry this risk.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tafamidis meglumine beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of tafamidis meglumine based on the data in the submission, the seriousness of transthyretin amyloidosis, and an adequately favorable benefit/risk profile.

Transthyretin amyloidosis is a rare, serious, progressive, life-threatening hereditary disease resulting in amyloid deposits that accumulate in multiple organ systems. This accumulation can lead to progressive peripheral polyneuropathy, cardiomyopathy, nephropathy, and gastrointestinal dysfunction. The most common clinical manifestation of ATTR-CM is heart failure, and it is also associated with small vessel disease (claudication, angina), conduction system disease (arrhythmias), pericardial disease, thromboembolisms, syncope or sudden death. Life expectancy from the onset of symptoms for ATTR-CM can range from 6 months to about 10 years.¹⁶ (b) (4)

(b) (4) randomized, double-blinded, trials demonstrate effectiveness of tafamidis meglumine for the treatment of ATTR-CM (b) (4) Study B3461028 evaluated patients with confirmed ATTR-CM due to variant or wild-type TTR and showed statistically significant effects of tafamidis meglumine 80 mg and 20 mg therapy compared to placebo based on all-cause mortality and frequency of cardiovascular-related hospitalizations. A significant treatment effect was observed in favor of tafamidis meglumine on functional capacity and health status as assessed by the 6MWT distance and KCCQ-OS score. (b) (4)

There are no risks associated with this drug that rise to inclusion in the Warnings and Precaution section, therefore, the proposed prescribing information does not include any Warnings and Precautions or Boxed Warnings. The risk of embryo fetal toxicity as well as monitoring recommendations and advice is included in the special populations section of the label. In addition, the Applicant will be required to complete a postmarketing requirement (PMR) to establish an observational study in women exposed to tafamidis meglumine during pregnancy to assess the risk of pregnancy complications and adverse effects on the developing fetus and neonate.

Therefore, based on the data available, and the favorable benefit-risk profile associated with tafamidis meglumine, this reviewer is not recommending a REMS for the management of the risks of tafamidis meglumine therapy.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for tafamidis meglumine to ensure the benefits outweigh the risks. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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