Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

New Drug Evaluation: Tafamidis

Date of Review: September 2019
Generic Name: tafamidis

End Date of Literature Search: July 2019
Brand Name (Manufacturer): Vyndaqel® and Vyndamax™ (Pfizer Inc)

Research Questions:

1. Is tafamidis safe and effective in improving clinically meaningful outcomes, including improvements in mortality, cardiovascular related hospitalizations, disease progression, quality of life, and survival in patients with cardiomyopathy associated with transthyretin-mediated amyloidosis (ATTR)?
2. Are there subgroups of patients with ATTR cardiomyopathy for which tafamidis is more effective or associated with fewer adverse events?

Conclusions:

- There is low quality evidence based on one phase 3 randomized controlled trial that tafamidis meglumine 20 mg and 80 mg decrease the incidence of all-cause mortality (29.5% vs. 42.9%; HR 0.70; 95% CI 0.51-0.96) and cardiovascular (CV) related hospitalizations (52.3% vs. 60.5%; RR 0.68; 95% CI 0.56-0.81) when analyzed in a combined, hierarchical fashion ($p<0.001$) in patients with ATTR cardiomyopathy who have heart failure with a history of hospitalizations.
- There is insufficient evidence of no difference in efficacy or adverse events between tafamidis meglumine 20 mg and tafamidis 80 mg.
- There is low quality evidence of no difference in discontinuations due to adverse events and serious adverse events between tafamidis meglumine and placebo in patients with cardiomyopathy of ATTR.
- Subgroup analysis suggests a greater benefit in patients with less severe heart failure. There was no difference in all-cause mortality and CV-related hospitalizations were higher in those with heart failure New York Heart Association (NYHA) class III compared to placebo. Patients with NYHA class IV were excluded from the study. The precise time course to benefit and timing of initiation in the course of the disease remain unknown.

Recommendations:

- Maintain tafamidis as a non-preferred medication.
- Modify prior authorization criteria for Drugs for Transthyretin-Mediated Amyloidosis to ensure appropriate use of tafamidis (**Appendix 2**).

Background:

Hereditary transthyretin amyloidosis (hATTR) is a rare, progressive, and fatal autosomal dominant disorder caused by misfolding deposits of transthyretin (TTR), a protein produced by the liver that normally functions as a transporter of thyroxine and retinol (vitamin A).[1] The disorder presents in a spectrum of clinical presentations due to amyloid deposits, including a predominantly neurologic phenotype (familial amyloid polyneuropathy [FAP]) and a predominantly cardiac phenotype (familial cardiomyopathy [FAC]). However, hATTR can present with both cardiac and neurologic manifestations. There are over 120 TTR reported mutations, with at least 22 mutations associated with cardiomyopathy. Some mutations are more strongly associated with polyneuropathy (V30M) and some

with cardiomyopathy.[2] The most common mutation in the U.S. is the Val122I mutation, which typically leads to cardiomyopathy, with an estimated prevalence of 3.0% to 4.0% in the African American population.[3] The second most common mutation in the U.S. is T60A, which causes a mixed neuropathy and cardiomyopathy presentation.[3] Deterioration in activities of daily living and ambulation are seen due to neuropathic changes as well as autonomic dysfunction. Additionally, ATTR can affect multiple organ systems resulting in weight loss, wasting, difficulty walking, and alternating constipation and diarrhea, often due to autonomic nerve involvement. Cardiac manifestations due to deposition of amyloid fibrils in the myocardium can include heart failure, arrhythmias, orthostatic hypotension or sudden death due to severe conduction disorders. Cardiomyopathy can be associated with both hereditary and wild-type transthyretin amyloidosis (ATTRwt). Median survival for patients with hATTR cardiomyopathy is 2.5 years and median survival of ATTRwt is 3.6 years.[4]

Standard of care for ATTR has been limited to liver transplantation and administration of transthyretin tetramer stabilizers in addition to symptomatic management of heart failure.[5] Liver transplant has been the treatment of choice for those with neuropathy but no cardiac involvement. Current treatment for cardiomyopathy focuses on managing the symptoms, including diuretics and pacemaker placement although heart transplantation may be appropriate in some patients. Inotersen and patisiran were recently approved for hATTR-associated polyneuropathy. However, there have been no agents FDA approved in the United States for the cardiomyopathy phenotype. Tafamidis is a TTR stabilizer that binds to TTR at the thyroxine binding sites, stabilizing the tetramer and slowing dissociation, the rate limiting step in amyloidogenesis. It is currently approved in Europe and several South American and Asian countries for early stage hATTR polyneuropathy. It was not approved in the U.S. in 2012 due to limited efficacy data. This is now the first Food and Drug Administration (FDA) approved drug for cardiomyopathy of ATTR and is available as two formulations (tafamidis meglumine and tafamidis free acid). Only the meglumine form was studied in phase 3 trials and the 2 formulations are not substitutable on a per mg basis.

The onset of symptoms of cardiomyopathy is usually greater than 60 years.[6] It is believed that this disease is widely underdiagnosed and may be the fourth most common cause of heart failure.[4] The goal of treatment in cardiomyopathy of ATTR is to prevent death from cardiac causes (heart failure, myocardial infarction, sudden cardiac death) and to decrease symptom burden (dyspnea, orthostatic hypotension, atrial fibrillation).

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Tafamidis was FDA-approved based on one phase 3 randomized controlled trial comparing pooled tafamidis meglumine (20 mg and 80 mg; n=264) to matching placebo (n=177) over 30 months in patients with heart failure due to confirmed (by biopsy) transthyretin amyloidosis.[7] The majority of patients had New York Heart Association (NYHA) Class II or III heart failure (67%), were male and had wild-type ATTR cardiomyopathy (75%). The primary outcome was all-cause mortality, followed by cardiovascular (CV) related hospitalizations, analyzed in a hierarchical fashion using the Finkelstein-Schoenfeld (FS) method. Comparisons were based on pooled tafamidis treatment groups versus placebo. Using the FS method, each subject is compared to every other subject within each stratum in a pair-wise manner for trial outcomes and ranked. Mortality carries a higher importance in ranking that does CV hospitalization. Thus, the pairwise comparison proceeds in hierarchical fashion using all-cause mortality first, assigning a +1 to the “better” subject and a -1 to the “worse” subject.[4] This approach was used in response to the challenges posed by conducting clinical trials of rare diseases. However, it is difficult to interpret the results. The FS method combines both fatal and recurrent nonfatal events, but prioritizes fatal events, allowing for increased power.

Overall, the FS method demonstrated a statistically significant result for all-cause mortality followed by CV related hospitalizations when comparing pooled tafamidis to placebo ($p<0.001$), with a win ratio of 1.7 (95% CI 1.3 to 2.3).[7] The win ratio is the number of pairs of treated-patients "wins" divided by the number of placebo patient "wins". The FS is a test statistic, but not an easily interpretable summary of the results. Cox regression analyses also suggested a lower all-cause mortality with tafamidis compared to placebo (29.5% vs. 42.9%; HR 0.70; 95% CI 0.51-0.96).[7] This is based on the mean treatment effect of the study. The hazard ratio was not constant with respect to time, so it is difficult to calculate the number needed to treat per year. This effect was observed after approximately 18 months of therapy and was driven by CV death. Lastly, there was a significant reduction in patients with CV-related hospitalizations with tafamidis compared to placebo (52.3% vs. 60.5%; RR 0.68; 95% CI 0.56-0.81).[7]

Subgroup analysis suggests a larger effect size in those with less severe heart failure at baseline (NYHA class I or II). There was no significant difference in all-cause mortality in those with NYHA Class III and a worse effect from tafamidis compared to placebo for CV hospitalizations.[7]There was also a statistically significant improvement in quality of life, measured by the Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-QS) with an increase of 13.7 points from baseline compared to placebo.[7] A 5-point difference is thought to be clinically meaningful.[4]

There were unequal and high rates of overall attrition between pooled tafamidis (34%) and placebo (52%), increasing the risk of attrition bias. Attrition was mostly due to death and withdrawal by subject that was not further clarified. There did not appear to be a dose effect and the two doses had similar efficacy. However, the approved dose is 80 mg based on greater TTR tetramer stabilizer and no obvious different in toxicities seen in the phase 3 trial. TTR stabilization is not an acceptable surrogate endpoint to establish efficacy.[4] Additionally, approximately 80% of the study population was white. However, the prevalence of cardiomyopathy due to ATTR is approximately 3-4% in U.S. African Americans and is negligible in the Caucasian population.[6] Twenty four percent of randomized patients had the most common mutations (Val122Ile, Thr60Ala, and Ile68Leu). There are no data available on the use of tafamidis post-liver transplantation.

Tafamidis is approved as two formulations that are not equivalent per mg dose. Tafamidis meglumine (Vyndaqel®) 80 mg is approved based on the phase 3 trials. Tafamidis free acid (Vyndamax™) 61 mg was also approved based solely on bioequivalence/bioavailability studies to the 80 mg.[4]

Clinical Safety:

There were no significant differences in treatment emergent serious adverse events between tafamidis 20 mg (75%), 80 mg (75.6%) and placebo (79.1%). The most common serious adverse events were cardiac disorders, which reflect the underlying disease progression. There were also similar rates of discontinuations due to adverse events (**Table 2**). No adverse events were included in the drug labeling. Post-marketing studies will be done to evaluate for adverse events related to hypothyroidism and falls or balance disorders due to some initial safety signals. There was also a slight increase in infection-related adverse events with tafamidis 80 mg compared to placebo, with rates of pneumonia adverse events of 5.3, 6.3 and 8.0 per 100 patient years in placebo, 20 mg and 80 mg arms respectively.[4] However, there were no differences in serious adverse events related to pneumonia.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) All-cause mortality
2) Hospitalizations
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) All-cause mortality
2) Cardiovascular-related hospitalizations

Table 1. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Tafamidis is a selective stabilizer of TTR. Tafamidis binds to TTR at the thyroxine binding sites, stabilizing the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.
Oral Bioavailability	N/A
Distribution and Protein Binding	The apparent steady state volume of distribution of tafamidis is approximately 18.5 liters. Plasma protein binding of tafamidis is >99% in vitro.
Elimination	59% recovered unchanged in feces, 22% in urine as glucuronide metabolite
Half-Life	49 hours
Metabolism	Not fully characterized; glucuronidation has been observed

Abbreviations: N/A: not available; TTR: transthyretin

Table 2. Comparative Evidence Table.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.ATTR-ACT[7] Phase 3, MC, PD, PC, DB RCT	1. Pooled tafamidis group: a. Tafamidis 20 mg daily b. Tafamidis 80 mg daily 2. Placebo Over 30 months	Demographics: 74 y/o, 90% male, 80% white, 75% ATTRwt Key Inclusion Criteria: Heart failure, evidence of cardiac amyloid by ECHO and interventricular septal wall thickness > 12 nm, presence of amyloid deposits in biopsy tissue and TTR precursor protein identification, NT-proBNP ≥ 600 pg/ml, 6MWT > 100 meters Key Exclusion Criteria: NYHA class IV HF, light-chain amyloidosis, liver or heart transplantation, cardiac device, GFR < 25 ml/min, LFTs > 2 x ULN, mBMI < 600, concurrent treatment with NSAIDs, doxycycline, CCBs or digitalis, significant drug or alcohol abuse within last 5 years, HIV, HBV, HCV, males or females of childbearing potential unwilling	ITT: 1. 264 2. 177 PP: 1. 173 2. 85 Attrition: 1. 52 2. 54	Primary Outcome: All-cause death + CV hospitalization (FS method): Test statistic: 3.44 P value 0.0006 Secondary Outcomes: All-cause mortality 1. 78 (29.5%) 2. 76 (42.9%) HR 0.70; 95% CI 0.51 to 0.96 Patients with CV-related hospitalizations: 1. 107 (60.5%) 2. 138 (52.3%) RR 0.68; 95% CI 0.56-0.81 *p-values not provided	ARR 13.4%/ NNT 8 ARR 8.2%/ NNT 13	Discontinuations due to adverse events: 1.17 (6.4%) 2. 11 (6.2%) NS P Value and 95% CI NR	NS	**Risk of Bias (low/high/unclear)**: Selection Bias: low; interactive response technology used for randomization and allocation concealment. Baseline characteristics similar between groups. Performance Bias: low; double-blinded; matching placebo Detection Bias: unclear blinding of outcome assessors Attrition Bias: high; mITT analysis done pooling both tafamidis dose groups. mITT includes all subjects who received at least one dose of medication and who had at least 1 post baseline efficacy evaluation. High and unequal attrition between tafamidis (34%) and placebo (52%). Reporting Bias: low; all outcomes reported Other Bias: unclear; funded by Pfizer. **Applicability**: Patient: significant exclusion criteria limits generalizability; mostly white (80%) males, while most common variant is present in 3 to 4% of blacks worldwide. 24% had the most common genetic mutations in the U.S. Intervention: 80 mg dose selected based on PK studies demonstrating maximal TTR stabilization with 80 mg. There did not appear to be a dose effect and the two doses had similar efficacy. TTR stabilization is not an acceptable surrogate endpoint to establish efficacy. Comparator: placebo appropriate; no other approved agents for comparison

		to use 2 methods of contraception, prior MI						Outcomes: Primary analysis used a hierarchical combination of all-cause mortality and frequency of all-cause hospitalization. Both tafamidis groups pooled and compared to placebo using the Finkelstein-Schoenfeld method Setting: multicenter; 60 sites in 13 countries (63% of patients enrolled at site in U.S).

Abbreviations [alphabetical order]: 6MWT = 6 minute walk test; ARR = absolute risk reduction; ATTR = transthyretin-mediated amyloidosis; ATTRwt = transthyretin-mediated amyloidosis wild type; CCB = calcium channel blocker; CI = confidence interval; CV = cardiovascular; DB = double blind; ECHO = echocardiogram; HIV: human immunodeficiency virus; FS = Finkelstein–Schoenfeld; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HF = heart failure ITT = intention to treat; LFT = liver function test; MC = multicenter; MI = myocardial infarction; mBMI = modified body mass index; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NSAID = nonsteroidal anti-inflammatory; NYHA = new York heart association; NR = not reported; PC = placebo controlled; PD = parallel-design; PK = pharmacokinetic; PP = per protocol; RCT = randomized controlled trial; RR: relative risk; TTR: transthyretin; ULN = upper limit of normal; U.S. = united states

References:

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2. Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. *BMC neurology.* 2017;17(1):181.
3. Donnelly JP, Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. *Cleveland Clinic journal of medicine.* 2017;84(12 Suppl 3):12-26.
4. FDA Center for Drug Evaluation and Research. Tafamidis Cilnical Review. Application Number: 211996Orig1s000. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211996Orig1s000,%20212161Orig1s000TOC.cfm.
5. Plante-Bordeneuve V. Update in the diagnosis and management of transthyretin familial amyloid polyneuropathy. *Journal of neurology.* 2014;261(6):1227-1233.
6. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation.* 2012;126(10):1286-1300.
7. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *The New England journal of medicine.* 2018;379(11):1007-1016.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYNDAQEL and VYNDAMAX safely and effectively. See full prescribing information for VYNDAQEL and VYNDAMAX.

VYNDAQEL® (tafamidis meglumine) capsules, for oral administration
Initial U.S. Approval: 2019

VYNDAMAX™ (tafamidis) capsules, for oral administration
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

VYNDAQEL and VYNDAMAX are transthyretin stabilizers indicated for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage is either:

- VYNDAQEL 80 mg orally once daily, or
- VYNDAMAX 61 mg orally once daily (2.1)
- VYNDAMAX and VYNDAQEL are not substitutable on a per mg basis. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: Tafamidis meglumine 20 mg and tafamidis 61 mg. (3)

CONTRAINDICATIONS

None. (4)

ADVERSE REACTIONS

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*. (5)

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2019

Drugs for Transthyretin-Mediated Amyloidosis (ATTR)

Goal(s):

- To limit utilization of medications for transthyretin mediated amyloidosis (ATTR) to FDA-approved indications and in populations with proven safety.

Length of Authorization:

Up to 6 months

Requires PA: (Both pharmacy and physician-administered claims)

- All medications indicated for ATTR

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: FDA approved therapies for ATTR amyloidosis

Drug	Indication
Inotersen	Polyneuropathy of hereditary ATTR
Patisiran	Polyneuropathy of hereditary ATTR
Tafamidis	Cardiomyopathy of ATTR (hereditary and wild type)

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
4. Is this an FDA approved indication of ATTR amyloidosis supported by transthyretin mutation proven by genetic testing (See Table 1)?	**Yes**: Go to #5 Document Genotype: _____	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have clinical signs and symptoms of disease (peripheral/autonomic neuropathy, motor disability, cardiovascular dysfunction)?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for or is the patient on concurrent use of more than one ATTR therapy (including diflunisal)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7
7. Has the patient had a liver transplantation?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is the request for patisiran or inoteren?	**Yes:** Go to #9	**No:** Go to #16
9. Is baseline disease severity documented (polyneuropathy disability (PND) score and Familial amyloid polyneuropathy (FAP) stage)?	**Yes:** Document and Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Was the medication prescribed or in consultation with a neurologist?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Is the patient on Vitamin A supplementation or have a documented normal level?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the request for patisiran?	**Yes**: Approve for 6 months	**No**: Go #13
13. Is the request for inotersen?	**Yes:** Go to # 14	**No:** Go to #16

Approval Criteria		
14. Has a baseline platelet count been obtained in the previous 3 months and are platelets ≥ 125 X 10^9/L?	**Yes:** Go to #15 Document baseline platelet count:_____ Date of Lab:_____	**No:** Pass to RPh. Deny; medical appropriateness.
15. Has baseline renal function been evaluated in the previous 3 months?	**Yes:** Approve for 6 months Document baseline serum creatinine and BUN:_____ Date of Lab:_____	**No:** Pass to RPh. Deny; medical appropriateness
16. Is the request for tafamidis?	**Yes:** Go to #17	**No:** Go to #19
17. Was the medication prescribed or in consultation with a cardiologist?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness.
18. Does the patient have a medical history of heart failure (NYHA class I-III) with at least one prior hospitalization for heart failure?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
19. Is the request for a newly approved hATTR therapy and does the indication match the FDA approved indication?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient had a documented response to treatment including at least one of the following: a. Improved neurologic impairment b. Improved motor function c. Improved quality of life d. Improved cardiac function	**Yes:** Go to #2	**No:** Pass to RPh; Deny (medical appropriateness)

Renewal Criteria		
2. Is the prescribed medication tafamidis?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Has the patient experienced stabilization OR improvement from baseline in one of the following: a. Baseline polyneuropathy disability (PND) score b. Familial amyloid polyneuropathy (FAP) stage	**Yes:** Go to #4	**No:** Pass to RPh; Deny (medical appropriateness)
4. Is the renewal for inotersen?	**Yes:** Go to #5	**No:** Approve for 12 months
5. Does the patient have a platelet count ≥ 100 X 10^9/L?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 9/19; 7/19 (MH)
Implementation: 11/1/19