Drug Monograph

Drug/Drug Class:	**Vyndaqel® (tafamidis meglumine) Capsule / Transthyretin Stabilizer**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Vyndaqel is available as a liquid-filled capsule containing 20 mg tafamidis meglumine. Distributed by: Pfizer Inc., New York, NY 10017
Summary of Findings:	The efficacy of Vyndaqel was established in a randomized, double-blind, multicenter, placebo-controlled Phase III trial of 441 patients with wild type or hereditary transthyretin-mediated amyloidosis. Patients were randomized to either daily Vyndaqel or placebo. The primary endpoints were all-cause mortality and frequency of cardiovascular-related hospitalizations. Treatment with Vyndaqel resulted in a significant reduction (p = 0.0006) in all-cause mortality and frequency of cardiovascular-related hospitalizations in the Vyndaqel group vs. placebo. The percentage of patients alive at month 30 was 70.5% and 57.1% for the Vyndaqel and placebo groups, respectively. The mean number of cardiovascular-related hospitalizations (per patient per year) among those alive at month 30 was 0.297 and 0.455 for Vyndaqel and placebo groups, respectively.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☒ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1-2]

Transthyretin-mediated amyloidosis (ATTR-CM) is a rare, life-threatening disease characterized by the buildup of abnormal deposits of misfolded protein called amyloid in the heart and is defined by restrictive cardiomyopathy and progressive heart failure. Symptoms include shortness of breath, fatigue, and peripheral edema. Often the disease is diagnosed only after symptoms have become severe. There are two sub-types of ATTR-CM: hereditary and wild type. Hereditary ATTR-CM is caused by an inherited mutation in the transthyretin gene that causes the transthyretin protein to become unstable and misfolded. V122I is the most common mutation and in the United States predominately affects African Americans or people of African descent as early as their 50's. Wild-type ATTR-CM is associated with aging and there is no inherited mutation. A majority of patients with ATTR-CM have wild type, which usually affects men after age 60. It is estimated that the prevalence of ATTR-CM is approximately 100,000 people in the U.S. however only 1 to 2% of those patients are diagnosed today.

Dosage Form [3]

Vyndaqel is available as a liquid-filled capsule containing 20 mg tafamidis meglumine.

Manufacturer [3]

Distributed by: Pfizer Inc., New York, NY 10017

Indication(s) [3]

Vyndaqel is indicated for treatment of the cardiomyopathy of wild type or hereditary ATTR-CM in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Tafamidis is a transthyretin (TTR) stabilizer that selectively binds to TTR at the thyroxine binding sites and stabilizes the tetramer of the TTR transport protein, slowing monomer dissociation into monomers which is the rate-limiting step in the amyloidogenic process.

Pharmacokinetics:

	Vyndaqel
Time to Peak	4 hours
Protein Binding	Transthyretin: >99.9%
Volume of Distribution	18.5 L
Metabolism	Not fully established; glucuronidation has been observed
Excretion	Urine: 22% (glucuronide metabolite)

	Feces: 59% (unchanged)
Half-life	49 hours

Clinical Trials Experience

STUDY DESIGN	Phase III randomized, double-blind, multicenter, placebo-controlled trial (n = 441)
INCLUSION CRITERIA	• 18 to 90 years of age • Medical history of Heart Failure (HF) with at least 1 prior hospitalization for HF or clinical evidence of HF (without hospitalization) requiring treatment with a diuretic for improvement • Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm • Presence of amyloid deposits in biopsy tissue and presence of a variant TTR genotype and/or TTR precursor protein
EXCLUSION CRITERIA	• A New York Heart Association (NYHA) classification of IV • Presence of primary (light chain) amyloidosis • Prior liver or heart transplantation or implanted cardiac mechanical assist device
TREATMENT REGIMEN	Patients were randomized to receive 80 mg of Vyndaqel, 20 mg of Vyndaqel, or placebo for 30 months
RESULTS	The primary endpoints were all-cause mortality and frequency of cardiovascular-related hospitalizations. The primary endpoint analysis demonstrated a significant reduction (p = 0.0006) in all-cause mortality and frequency of cardiovascular-related hospitalizations in the pooled Vyndaqel groups vs. placebo. The percentage of patients alive at month 30 was 70.5% and 57.1% for the pooled Vyndaqel and placebo groups, respectively. The mean number of cardiovascular-related hospitalizations (per patient per year) among those alive at month 30 was 0.297 and 0.455 for Vyndaqel and placebo, respectively. Individual components of the primary endpoint analysis also demonstrated a relative reduction in the risk of all-cause mortality and frequency of cardiovascular-related hospitalization of 30% (p = 0.026) and 32% (p < 0.0001), respectively, with Vyndaqel vs. placebo.
SAFETY	The frequency of adverse events in patients treated with Vyndaqel was similar to that with placebo.

Contraindications [3]

- None.

Warnings and Precautions [3]

- Pregnancy: Based on animal studies, Vyndaqel may cause fetal harm.
- Lactation: Patients should be advised not to breastfeed.

Adverse Effects [3]

- There are no adverse reactions listed in the manufacturer's labeling.

Drug Interactions [3]

- BCRP Substrates: Tafamidis inhibits breast cancer resistant protein (BCRP) in vitro and may increase exposure of substrates of this transporter (e.g., methotrexate, rosuvastatin, imatinib) following Vyndaqel. Dose adjustment may be needed for these substrates.

Dosage and Administration [3]

- 80 mg orally once daily.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Tafamidis	Vyndaqel	Pfizer	4 - 20 mg capsules	$18,750 / 30 day supply

** Wholesale Acquisition Cost

Conclusion

Vyndaqel is the first FDA-approved treatment for ATTR-CM. It works by selectively binding to transthyretin, stabilizing the tetramer of the transthyretin transport protein and slowing the formation of amyloid that causes ATTR-CM. The efficacy of Vyndaqel was established in a double-blind study in 441 patients with wild type or hereditary ATTR-CM. Treatment with Vyndaqel demonstrated a significant reduction in mortality and frequency of cardiovascular-related hospitalizations. There are no known adverse reactions associated with Vyndaqel use.

Recommendation

The Division recommends adding this drug as a new clinical edit.

References

1) Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis and treatment. *Trends Cardiovasc Med*. 2017;1050-1738.
2) Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation*. 2012;126(10):1286-1300.
3) Product Information: Vyndaqel® (tafamidis). Pfizer, Inc., New York, NY 10017.
4) Tafamidis: Drug Information. Lexi-Drugs. Wolters Kluwer Clinical Drug Information Inc.
5) Mauer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with

Transthyretin Amyloid Cardiomyopathy. *N Engl J Med.* 2018 Sept 13;379(11):1007-1016.

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