PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrVYNDAQEL™

tafamidis meglumine capsules

20 mg, Oral

Selective stabilizer of transthyretin

Pfizer Canada ULC
17,300 TransCanada Highway
Kirkland, Quebec H9J 2M5

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VYNDAQEL (tafamidis meglumine) is indicated for:

the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): Safety and efficacy were demonstrated in this population.

2 CONTRAINDICATIONS

VYNDAQEL is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Dosage Adjustment

The recommended dose of VYNDAQEL is 80 mg tafamidis meglumine (administered as four 20 mg capsules) orally once daily.

The dose may be reduced to 20 mg if not tolerated (see Clinical Trials).

Special populations

Pregnant Women

VYNDAQEL should not be used during pregnancy (see Warnings and Precautions).

Women of childbearing potential should use appropriate contraception when taking VYNDAQEL and continue to use contraception for 1-month after stopping treatment.

Pediatrics (<18 years of age)
VYNDAQEL is not indicated in the pediatric population.

Geriatrics (≥65 years of age)
No dosage adjustment is required for elderly patients (≥65 years). Of the total number of patients in the ATTR-CM clinical study (n=441), 90.5% were 65 and over, with a median age of 75 years.

Renal or hepatic impairment
VYNDAQEL has not been studied in patients with severe hepatic impairment and use is not recommended in these patients. No dosage adjustment is required for patients with mild or moderate hepatic impairment. Data are limited in patients with severe renal impairment. No dosage adjustment is required for patients with renal impairment.

3.2 Administration

The capsules should be swallowed whole and not crushed or cut. VYNDAQEL may be taken with or without food.

3.3 Missed Dose

If a dose is missed, the patient should take the dose as soon as remembered. If it is almost time for the next dose, the patient should skip the missed dose and take the next dose at the regularly scheduled time.

4 OVERDOSAGE

There is minimal clinical experience with overdose. During clinical trials, two patients diagnosed with ATTR-CM accidentally ingested a single tafamidis meglumine dose of 160 mg without adverse events. The highest dose of tafamidis meglumine given to healthy volunteers in a clinical trial was 480 mg as a single dose.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule 20 mg: Each soft gelatin capsule (filled with a white to pink suspension) contains 20 mg of micronized tafamidis meglumine (equivalent to 12.2 mg tafamidis)	Ammonium hydroxide 28%, brilliant blue FCF, carmine, gelatin, glycerin, iron oxide (yellow), polyethylene glycol 400, polysorbate 80, polyvinyl acetate phthalate, propylene glycol, sorbitan monooleate, sorbitol, and titanium dioxide.

VYNDAQEL 20 mg: yellow, opaque, oblong (approximately 21 mm) capsule printed with “VYN 20” in red. 120 capsules (one month supply) supplied in 4 intermediary cartons. Each intermediary carton contains 3 blister cards, with 10 capsules each.

6 WARNINGS AND PRECAUTIONS

General

No studies have been conducted in organ transplant patients. The efficacy and safety of VYNDAQEL in organ transplant patients has not been established. Tafamidis is not recommended in these patients.

Carcinogenesis and Mutagenesis

Carcinogenesis

There was no evidence of an increased incidence of neoplasia in the transgenic (Tg)-rasH2 mouse following repeated daily administration for 26 weeks at daily doses of 0, 10, 30 or 90 mg/kg. There was no evidence of increased incidence of neoplasia in a 2-year

carcinogenicity study in rats at exposures 18-times the human AUC at the clinical dose of 80 mg tafamidis meglumine.

Mutagenesis
There was no evidence of mutagenicity or clastogenicity in vitro, and an in vivo rat micronucleus study was negative.

Driving and Operating Machinery

VYNDAQEL has not been shown to influence the ability to drive and use machines.

Hepatic/Biliary/Pancreatic

VYNDAQEL has not been studied in patients with severe hepatic impairment and use is not recommended in these patients.

Renal

Limited data are available in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min).

Sexual Health

Reproduction

Studies in animals have shown developmental toxicity. The potential risk for humans is unknown. VYNDAQEL should not be used during pregnancy.

Women of childbearing potential should use appropriate contraception when taking VYNDAQEL and continue to use contraception for 1-month after stopping treatment.

6.1 Special Populations

6.1.1 Pregnant Women

There are no adequate and well-controlled clinical studies with the use of VYNDAQEL in pregnant women. Studies in animals have shown developmental toxicity. The potential risk for humans is unknown. VYNDAQEL should not be used during pregnancy.

6.1.2 Breast-feeding

There are no clinical data available to support the presence of tafamidis in human breast milk. Nonclinical data demonstrates that tafamidis is secreted in the milk of lactating rats. When a drug is present in animal milk, it is likely the drug will be present in human milk. The effect of VYNDAQEL on nursing infants after administration to the mother has not been studied. Based on findings from animal studies which suggest the potential for serious adverse reactions in the breastfed infant, VYNDAQEL should not be used by nursing women.

6.1.3 Pediatrics (<18 years of age)

VYNDAQEL is not indicated and should not be prescribed in the pediatric population.

7 ADVERSE REACTIONS

7.1 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data across clinical trials reflect exposure of 377 ATTR-CM patients to either 20 mg or 80 mg (administered as four 20 mg capsules) of VYNDAQEL daily for an average of 24.5 months (ranging from 1 day to 111 months). The population included adult patients diagnosed with ATTR-CM with baseline NYHA (New York Heart Association) Class I, Class II or Class III respectively at 9.1%, 61.4%, and 29.5% in the pooled tafamidis arm and at 7.3%, 57.1% and 35.6%, respectively on placebo. The mean age was approximately 75 years (ranging from 46 years to 91 years of age); >90% were male, and approximately 82% were Caucasian (see Study Results **Table 5: Patient Demographics and Baseline Characteristics)**.

Adverse events were assessed from ATTR-CM clinical trials with VYNDAQEL including a 30-month placebo-controlled trial in patients diagnosed with ATTR-CM. The frequency of adverse events in patients treated with VYNDAQEL 20 mg (n=88) or 80 mg (n=176; administered as four 20 mg capsules) was comparable to placebo (n=177). Listed below are all causality adverse events reported in the pivotal clinical trial.

A similar proportion of VYNDAQEL-treated patients compared to placebo discontinued due to an adverse event in the 30-month placebo-controlled trial in patients diagnosed with ATTR-CM [12 (6.8%), 5 (5.7%), and 11 (6.2%)] from the tafamidis meglumine 80 mg, tafamidis meglumine 20 mg, and placebo groups, respectively].

The most frequently reported Treatment emergent Serious Adverse Events (TESAEs) in the tafamidis 80 mg, 20 mg and placebo groups respectively were condition aggravated (22.7%, 23.9% and 32.8%); cardiac failure (19.3%, 18.2%, and 22.6%), cardiac failure congestive (11.9%, 15.9% and 17.5%), cardiac failure acute (13.1%, 4.5% and 9.6%), fall (5.1%, 5.7% and 2.8%) and syncope (3.4%, 0%, 5.6%).

Treatment emergent Adverse Events (TEAEs) with a higher incidence in the tafamidis 80 mg and 20 mg treatment group than placebo (≥2x placebo and reported by ≥4 patients) respectively, included cystitis (3.4%, 2.3% and 0%), sinusitis (5.7%, 5.7% and 0.6%), asthenia (10.2%, 12.5% and 6.2%), balance disorder (8.5%, 2.3% and 1.1%) and cataract (5.1%, 3.4% and 1.1%).

The most commonly reported TEAEs (≥10%) in the tafamidis 80 mg and/or 20 mg groups that occurred at rates higher than placebo are as follows (80 mg, 20 mg and placebo, respectively): atrial fibrillation (19.9%, 18.2% and 18.6%), cardiac failure (26.1%, 34.1% and 33.9%), cardiac failure acute (13.6%, 4.5% and 9.6%), cardiac failure congestive (12.5%, 19.3% and 18.6%), asthenia (10.2%, 12.5% and 6.2%), edema peripheral (17.0%, 19.3% and 17.5%), bronchitis (11.9%, 10.2% and 10.7%), pneumonia (13.1%, 11.4% and 9.6%), fall (24.4%, 30.7% and 23.2%), muscle spasms (8.5%, 11.4% and 7.9%), pain in extremity (15.3%, 6.8% and 11.3%), insomnia (11.4%, 13.6% and 12.4%), hematuria (5.7%, 11.4% and 9.6%), cough (11.9%, 18.2% and 16.9%), and hypotension (10.8%, 13.6% and 10.7%).

Incidence of hypothyroidism was reported in 6.8%, 5.7% and 5.6% patients in the tafamidis 80 mg, 20 mg and placebo groups, respectively.

7.2 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The incidence of thyroxine abnormality <0.8 x LLN was greater in the tafamidis 80 mg group (29.7%) than in the tafamidis 20 mg (12.3%) and placebo (4.5%) groups. No clinically meaningful shifts in free thyroxine or thyroid stimulating hormone values were observed, and no corresponding signal in thyroid dysfunction was observed in the analysis of TEAEs (see Adverse Reactions for cases of hypothyroidism).

Low neutrophil count (<0.8 x LLN) was more frequent with tafamidis treatment than with placebo (1.9% tafamidis 80 mg, 1.2% tafamidis 20 mg, 0.6% placebo).

Elevated liver function tests were more frequent in the tafamidis 80 mg group (3.4%) than in the tafamidis 20 mg (2.3%) and placebo (1.1%) groups.

8 DRUG INTERACTIONS

8.1 Overview

In vitro studies:

Cytochrome P450 Enzymes: Tafamidis induces CYP2B6 and CYP3A4 and does not induce CYP1A2.
*T*afamidis does not inhibit cytochrome P450 enzymes CYP1A2, CYP3A4, CYP3A5, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and moderately inhibits CYP2C8.

UDP glucuronosyltransferase (UGT): Tafamidis inhibits intestinal activities of UGT1A1 but neither induces nor inhibits other UDP glucuronosyltransferase (UGT) systemically.

Transporter Systems: Tafamidis inhibits breast cancer resistant protein (BCRP). In vitro studies and model predictions show that tafamidis has a potential to inhibit the organic anion transporters OAT1 and OAT3 at clinically relevant concentrations. Tafamidis did not show a potential to inhibit Multi-Drug Resistant Protein (MDR1) (also known as P-glycoprotein; P-gp), organic cation transporter OCT2, multidrug and toxin extrusion transporters MATE1 and MATE2K and, organic anion transporting polypeptide OATP1B1 and OATP1B3.

8.2 Drug-Drug Interactions

Table 2 - Established or Potential Drug-Drug Interactions

Drug Name	Source of Evidence	Effect	Clinical comment
CYP3A4 substrates (e.g., midazolam, triazolam)	*In vivo*	Tafamidis (20 mg) did not affect the PK of CYP3A4 substrate midazolam; the effect of 80 mg has not been studied.	In vitro, tafamidis induces CYP3A4 and may decrease exposure of substrates of this CYP enzyme at the higher dose of 80 mg. Caution should be exercised when VYNDAQEL is co-administered with CYP3A4 substrates. Dose adjustment may be needed for these substrates.

Drug Name	Source of Evidence	Effect	Clinical comment
Substrates of breast cancer resistant protein BCRP (e.g., methotrexate, rosuvastatin, imatinib)	*In vitro*	Tafamidis inhibits BCRP systemically and in the GI tract and may increase exposure of substrates of this transporter.	Caution should be exercised when VYNDAQEL is co-administered with BCRP substrates. Dose adjustment may be needed for these substrates.
Substrates of organic anion transporters 1 (OAT1) and OAT3 (e.g., antiretroviral agents, diuretics, methotrexate, NSAIDs, olmesartan, pravastatin)	*In vitro*	In vitro data indicates that tafamidis has a potential to inhibit OAT1and OAT3 and may therefore decrease exposure of substrates of these transporters.	Caution should be exercised when VYNDAQEL is co-administered with OAT1 and OAT3 substrates. Dose adjustment may be needed for these substrates.

Interactions with other drugs have not been studied.

8.3 Drug-Food Interactions

No clinically significant differences in the pharmacokinetics of tafamidis were observed following administration of a high fat, high calorie meal.

8.4 Drug-Herb Interactions

No interaction studies have been performed evaluating the effect of herbal products on tafamidis.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 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.

9.2 Pharmacodynamics

A TTR stabilization assay was utilized as a pharmacodynamic marker and assessed the stability of the TTR tetramer under denaturation conditions. Tafamidis stabilized both the wild-type TTR tetramer and the tetramers of 14 TTR variants tested clinically after once-daily dosing. Tafamidis also stabilized the TTR tetramer for an additional 26 variants tested *ex vivo.*

The tafamidis 80 mg dose was selected based on maximal TTR % stabilization data from PK studies. The clinical relevance of a higher TTR stabilization is not known.

Cardiac Electrophysiology

At single dose of 400 mg, approximately 2.2 times the steady state peak plasma concentration (C_{max}) at the recommended dose, tafamidis does not prolong the QTc interval to any clinically relevant extent.

9.3 Pharmacokinetics

Table 3 - Summary of Tafamidis Meglumine Pharmacokinetic Parameters in Patients with ATTR-CM

	Tafamidis meglumine	C_{max} (µg/mL)	T_{max}[a] (h)	$t_{½}$ (h)	AUC_{tau} (µg*h/mL)	CL (L/h)	V_{ss} (L)
Steady-state mean[b]	20 mg, QD	3.00	1.75 (0.5, 10.5)	57	60.39	0.203	16.6
	80 mg, QD	11.99			241.50		

[a] Median (5^{th}, 95^{th} quantile) T_{max} values across 1000 simulated trials of n = 30 patients with ATTR-CM;
[b] Population PK estimates assuming 80 Kg body weight and ≥ 65 years of age across 1000 simulated trials of n = 30 patients with ATTR-CM;
CL = apparent oral clearance; V_{ss} = steady-state apparent oral volume of distribution

The pharmacokinetic profile of tafamidis was characterized in healthy volunteers (n = 333) and patients with transthyretin amyloidosis (n = 427). Steady-state PK parameters were estimated by a population PK analysis. Tafamidis apparent oral clearance was affected by age and body weight. Over the range of 57.5 to 93 kg (corresponding to the 10^{th} and 90^{th} percentile of the observed weights) the clearance changed from 0.85-fold to 1.14-fold relative to the median weight and it decreased by 14.5% in subjects ≥ 65 years of age compared to younger subjects.

Absorption:
After oral administration of VYNDAQEL once daily, the maximum peak concentration (C_{max}) is achieved at a median time (t_{max}) within 4 hours after dosing in the fasted state.

Concomitant administration of a high fat, high calorie meal altered the rate of absorption, but not the extent of absorption. These results support the administration of VYNDAQEL with or without food.

Distribution:
Tafamidis is highly protein bound (>99%) in plasma. The apparent steady-state volume of distribution is 16 liters.

Metabolism:
While there is no explicit evidence of biliary excretion of tafamidis in humans, based on preclinical data, it is suggested that tafamidis is metabolized by glucuronidation and excreted via the bile. This route of metabolism and excretion is likely in humans, as approximately 59% of the total administered dose is recovered in feces mostly as unchanged drug, and approximately 22% recovered in urine mostly as the glucuronide metabolite.

Elimination:
The mean half-life of tafamidis is approximately 49 hours. The apparent oral clearance of tafamidis is 0.228 L/hr. The degree of drug accumulation at steady state after repeated tafamidis daily dosing is approximately 2.5-fold greater than that observed after a single dose.

Special Populations and Conditions

Race: No clinically significant differences in the pharmacokinetics of tafamidis were observed based on race/ethnicity (Caucasian and Japanese).

Pediatrics: Tafamidis has not been studied and is not indicated in this population.

Hepatic Insufficiency: Pharmacokinetic data indicated decreased systemic exposure (approximately 40%) and approximately 68% increase of total clearance (0.52 L/h versus 0.31 L/h) of tafamidis meglumine in subjects with moderate hepatic impairment (Child-Pugh Class B) compared to healthy subjects. As TTR levels are lower in patients with moderate hepatic impairment than in healthy subjects, the exposure of VYNDAQEL relative to the amount of TTR would be sufficient for stabilization of the TTR tetramer in these patients.

Exposure to VYNDAQEL was similar between subjects with mild hepatic impairment (Child-Pugh Class A) and healthy subjects.

The pharmacokinetics of VYNDAQEL in patients with severe hepatic impairment (Child-Pugh Class C) is unknown.

Renal Insufficiency: VYNDAQEL has not specifically been evaluated in patients with renal impairment. Limited data are available in patients with severe renal impairment (CrCl ≤30 mL/min).

STORAGE, STABILITY AND DISPOSAL

Store VYNDAQEL at room temperature 15°C to 25°C.

PART II: SCIENTIFIC INFORMATION

10 PHARMACEUTICAL INFORMATION

Drug Substance

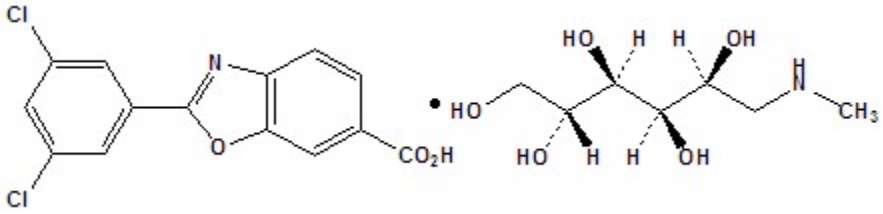
Common name: tafamidis meglumine

Chemical name: 2-(3,5-dichlorophenyl)-benzoxazole-6-carboxylic acid
mono (1-deoxy-1-methylamino-D-glucitol)

Tafamidis meglumine
The molecular formula is $C_{14}H_7Cl_2NO_3$ $C_7H_{17}NO_5$, and the molecular mass is 503.33 g/mol

Tafamidis free acid
The molecular formula is $C_{14}H_7Cl_2NO_3$, and the molecular mass is 308.12 g/mol

Structural formula:



Physicochemical properties: Tafamidis meglumine is a white to pink powder. It is slightly soluble in water and methanol.

Aqueous Solubility of Tafamidis Meglumine

Solution	Solubility (mg/mL)
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

11 CLINICAL TRIALS

11.1 Trial Design and Study Demographics

Table 4 - Summary of patient demographics for clinical trials in cardiomyopathy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
B3461028	Double-blind, placebo-controlled, randomized	Oral and 30 months	441 patients enrolled into the study n=177 in the placebo arm n=88 in the tafamidis meglumine 20 mg arm n=176 in the tafamidis meglumine 80 mg arm.	74.5 years (range: 46 to 88 years) in tafamidis-treated patients 74.1 years (range: 51 to 89 years) in placebo patients	Female and Male

11.2 Study Results

Efficacy was demonstrated in a multicenter, international, double-blind, placebo-controlled, randomized study in 441 patients with wild type or hereditary ATTR-CM.

Eligible patients had ATTR-CM confirmed by biopsy specimens obtained from cardiac and noncardiac sites and, in patients without ATTRm, by the presence of transthyretin precursor protein confirmed on immunohistochemical analysis, scintigraphy, or mass spectrometry.

Patients were randomized to either tafamidis meglumine 20 mg (n=88) or 80 mg [administered as four 20 mg tafamidis meglumine capsules] (n=176) or matching placebo (n=177) once daily, in addition to standard of care (e.g., diuretics) for 30 months. Treatment assignment was stratified by the presence or absence of a variant TTR genotype and by baseline NYHA Class. Transplant patients were excluded from this study.

Table 5: Patient Demographics and Baseline Characteristics

Characteristic	Pooled Tafamidis N=264	Placebo N=177
Age — year		
Mean (Standard Deviation)	74.5 (7.2)	74.1 (6.7)
Median (minimum, maximum)	75 (46, 88)	74 (51, 89)
Sex — number (%)		
Male	241 (91.3)	157 (88.7)
Female	23 (8.7)	20 (11.3)
TTR Genotype — number (%)		
ATTRm	63 (23.9)	43 (24.3)

Characteristic	Pooled Tafamidis N=264	Placebo N=177
ATTRwt	201 (76.1)	134 (75.7)
NYHA Class — number (%)		
NYHA Class I	24 (9.1)	13 (7.3)
NYHA Class II	162 (61.4)	101 (57.1)
NYHA Class III	78 (29.5)	63 (35.6)

Abbreviations: ATTRm = variant transthyretin amyloid, ATTRwt = wild type transthyretin amyloid, NYHA=New York Heart Association.

The primary analysis used a hierarchical combination applying the method of Finkelstein-Schoenfeld (F-S) to all-cause mortality and frequency of cardiovascular-related hospitalizations, which was defined as the number of times a subject is hospitalized for cardiovascular-related morbidity. The method compared each patient to every other patient within each stratum in a pair-wise manner that proceeded in a hierarchical fashion using all-cause mortality followed by frequency of cardiovascular-related hospitalizations when patients cannot be differentiated based on mortality.

This analysis demonstrated a significant reduction (p=0.0006) in all-cause mortality and frequency of cardiovascular-related hospitalizations in the pooled tafamidis meglumine 20 mg and 80 mg groups versus placebo (Table 6).

Table 6: Primary Analysis Using Finkelstein-Schoenfeld (F-S) Method of All-Cause Mortality and Frequency of Cardiovascular-Related Hospitalizations

Primary Analysis	Pooled Tafamidis N=264	Placebo N=177
Number (%) of Subjects Alive* at Month 30	186 (70.5)	101 (57.1)
Average Cardiovascular-related Hospitalizations 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	

* Heart transplantation and cardiac mechanical assist device implantation are considered indicators of approaching end stage. As such, these subjects are treated in the analysis as equivalent to death. Therefore, such subjects are not included in the count of "Number of Subjects Alive at Month 30" even if such subjects are alive based on 30 month vital status follow-up assessment.

The hazard ratio from the all-cause mortality Cox-proportional hazard model for pooled VYNDAQEL versus placebo was 0.70 (95% confidence interval [CI] 0.51, 0.96), indicating a 30% relative reduction in the risk of death relative to the placebo group (p=0.026).

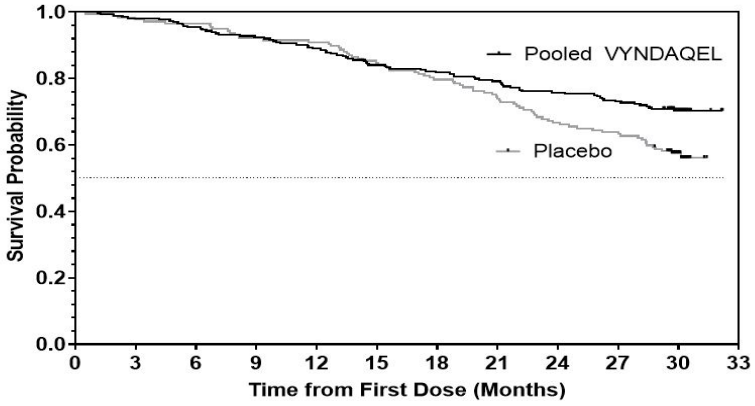
The difference in mortality events between groups was attributable to CV related events.

Overall, 20.8% of the pooled tafamidis and 33.3% of the placebo groups had CV-related deaths.

Non-CV-related deaths were reported in 5.3% of the pooled tafamidis and 4.7% of the placebo group.

A Kaplan-Meier plot of time to event all-cause mortality is presented in Figure 1.

Figure 1: All-Cause Mortality*



Subjects Remaining at Risk (Cumulative events)

Pooled	264	259	252	244	235	222	216	209	200	193	99	0
VYNDAQEL	0	5	12	20	29	42	48	55	64	71	76	78
Placebo	177	173	171	163	161	150	141	131	118	113	51	0
	0	4	6	14	16	27	36	46	59	64	75	76

*Heart transplants and cardiac mechanical assist devices treated as death. Hazard ratio from Cox proportional hazards model with treatment, TTR genotype (variant and wild type), and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors.

There were significantly fewer cardiovascular-related hospitalizations with tafamidis compared with placebo with a reduction in risk of 32% (Table 7).

Table 7: Cardiovascular-Related Hospitalization Frequency

	Pooled VYNDAQEL N=264	**Placebo N=177**
Total (%) Number of Subjects with Cardiovascular-related Hospitalizations	138 (52.3)	107 (60.5)
Cardiovascular-related Hospitalizations per Year*	0.48	0.70
Pooled VYNDAQEL vs Placebo Treatment Difference (Relative Risk Ratio)*	0.68	
p-value*	<0.0001	

*This analysis was based on a Poisson regression model with treatment, TTR genotype (variant and wild type), New York Heart Association (NYHA). Baseline classification (NYHA Classes I and II combined and NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by-NYHA baseline classification interaction terms as factors.

The treatment effect of tafamidis on functional capacity and health status was assessed by the 6-Minute Walk Test (6MWT) and the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score, respectively. A significant treatment effect favoring tafamidis was first observed at Month 6 and remained significant through Month 30 for both the 6MWT and the KCCQ-OS.

The Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score is composed of four domains including Total Symptoms (Symptom Frequency and Symptom Burden), Physical Limitation, Quality of Life, and Social Limitation. The Overall Summary score and domain scores range from 0 to 100, with higher scores representing better health status. The distribution for change from Baseline to Month 30 for KCCQ-OS shows that the proportion of patients with worse KCCQ-OS scores was lower for the pooled VYNDAQEL-treated group compared to placebo, and the proportion with improved scores was higher.

Results of the primary analysis, the components of the primary analysis, functional capacity (6MWT) and health status (KCCQ-OS) at Month 30, cardiovascular-related mortality, and TTR-stabilization at Month 1 were analyzed by individual doses (80 mg and 20 mg) compared to placebo.

In the pivotal trial, comparable TTR stabilization rates were seen for both the 20 mg and 80 mg doses at 12 months (83% and 88%, respectively).

Both tafamidis meglumine doses (80mg and 20mg) appeared to be as effective. However, the study was not powered to distinguish between doses. The hazard ratios from the all-cause mortality for the 80 mg and 20 mg tafamidis doses relative to placebo were 0.69 (95% CI 0.49, 0.98) and 0.72 (95% CI 0.45, 1.14), respectively. The relative risk ratios for CV-related hospitalization between the tafamidis 80 mg and 20 mg relative to placebo were 0.70 (95% CI 0.57, 0.86) and 0.66 (95% CI 0.51, 0.86).

The key secondary endpoints (6-minute walk test and the KCCQ-OS score) were also comparable between doses.

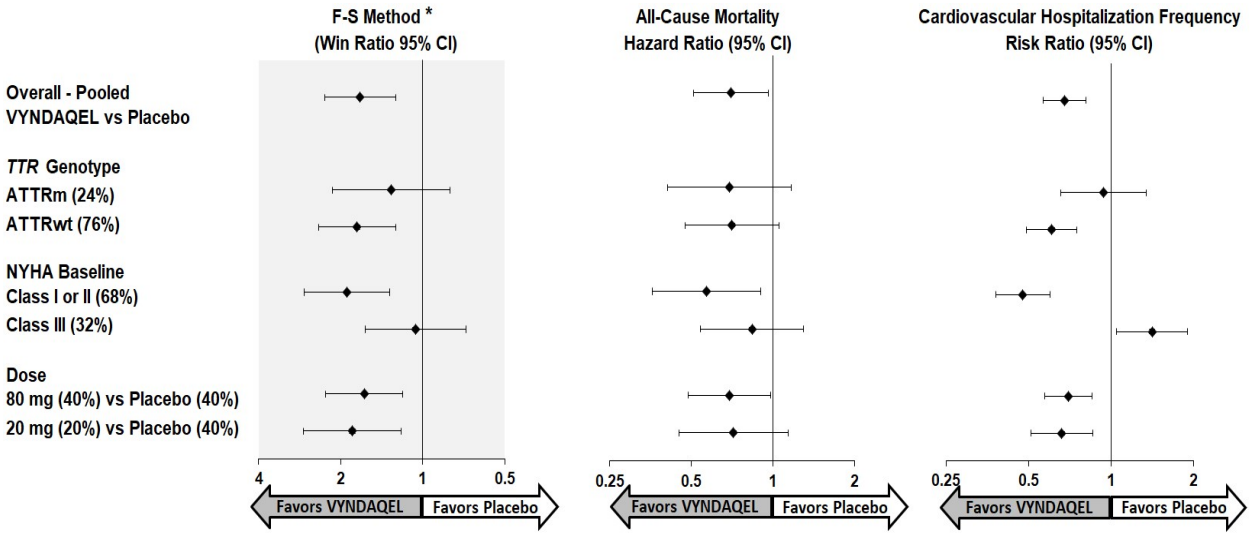
Potential benefit for the 80 mg dose was suggested in post hoc exploratory analyses of reduction of cardiac biomarker NT-proBNP at month 30 and reaching a difference from placebo at an earlier time point.

Results from F-S method represented by the win ratio for the combined endpoint and its components (all-cause mortality and frequency of CV-related hospitalization) favored tafamidis versus placebo across wild type, variant and NYHA Class I & II subgroups.

In NYHA Class III subgroup, the proportion of patients with CV-related hospitalizations were 76.9% vs 58.7% and CV mortality were 51.3% vs 49.2% for pooled tafamidis and placebo treatment groups respectively.

Analyses of 6MWT and KCCQ-OS favored tafamidis relative to placebo within each subgroup.

Figure 2: Results by Subgroup, Dose, and Components of Primary Analysis



Abbreviations: ATTRm = variant transthyretin amyloid, ATTRwt = wild type transthyretin amyloid, F-S = Finkelstein Schoenfeld, CI = Confidence Interval
*F-S results presented using win ratio (based on all-cause mortality and frequency of cardiovascular hospitalization) Win ratio is the number of pairs of treated-patient "wins" divided by number of pairs of placebo patient "wins". Heart transplants and cardiac mechanical assist devices treated as death.

There are no clinical data in patients of NYHA Class IV at baseline.

12 NON-CLINICAL TOXICOLOGY

The non-clinical program of tafamidis meglumine was based on conventional studies of safety pharmacology, pharmacodynamic and pharmacokinetic studies, repeat-dose toxicity, reproductive and developmental toxicity, carcinogenicity, genetic toxicity, phototoxicity, and immunotoxicity. Non-clinical toxicology findings which are relevant for the safe use of the drug and/or contribute to the understanding of a drug's toxicological profile are summarized below:

General toxicology and carcinogenicity
In repeat-dose toxicity and carcinogenicity studies, even though there was no evidence of neoplasia, the liver and/or kidney appeared as target organs for toxicity in the different species tested. Liver effects were observed at exposures approximately ≥0.7-times the human exposure at a dose of 80 mg tafamidis meglumine.

Significant non-neoplastic lesions were noted in the kidneys (nephrosis) and liver (centrilobular hypertrophy and single cell necrosis) in the Tg-rasH2 mice at dose levels ≥2.9-times the clinical dose of 80 mg tafamidis meglumine. Renal nephrosis was noted only in male (Tg)-rasH2 mice with a higher incidence and severity at 90 mg/kg/day and not observed at ≤30 mg/kg/day, with corresponding AUC_{24} values, which was ≤2.9-times the human steady state AUC_{24} at the clinical dose of 80 mg tafamidis meglumine.

Fertility
There were no effects of tafamidis meglumine on fertility, reproductive performance, or mating behavior in the rat at any dose up to 30 mg/kg (human equivalent dose of tafamidis meglumine greater than 4.8 mg/kg/day). Rats were dosed daily (5, 15, and 30 mg/kg/day) prior to cohabitation (for at least 15 days for females and 28 days for males), throughout the cohabitation period to the day prior to termination of males and through to implantation of females (Gestation Day 7). No adverse effects were noted on male rats at any dose. Females had statistically significant weight loss and decreased feed consumption in the highest dose group during the first week of dosing.

The paternal and maternal no observed effect level for reproductive toxicity of tafamidis meglumine is 30 mg/kg/day, 6.9-times the clinical dose of 80 mg tafamidis meglumine.

Placental and milk transfer

Pregnant and lactating female rats were administered repeated daily oral doses of tafamidis meglumine (15 mg/kg/day) followed by a single oral gavage dose of ^{14}C-tafamidis meglumine on Lactation Day 4 or 12. Radiolabelled material was observed in blood and fetal tissues and distribution was widespread by the first timepoint analyzed, suggesting that dose-related material had crossed the placental barrier. The concentrations in fetal tissue were generally higher on Day 19 of gestation as compared to Day 15 of gestation. Radioactivity was observed in milk by 1 hour post-dose and increased thereafter. The ratio of the highest radioactivity associated with ^{14}C-tafamidis meglumine in milk (8 hours post-dose) vs. plasma (1 hour post-dose) was approximately 1.6 on Day 12, indicating tafamidis meglumine is transferred to milk after oral administration.

Developmental toxicity

In an embryo-fetal developmental toxicity study in rabbits, oral administration of tafamidis meglumine (0, 0.5, 2, and 8 mg/kg/day) throughout organogenesis resulted in increased embryofetal mortality, reduced fetal body weights, and an increased incidence of fetal malformations at 8 mg/kg/day (approximately 9 times the human exposure of 80 mg tafamidis meglumine based on AUC), which was also maternally toxic. Increased incidences of fetal skeletal variations were observed at doses ≥0.5 mg/kg/day (approximately equivalent to the human exposure of 80 mg tafamidis meglumine based on AUC).

In an embryo-fetal development toxicity study in rats, oral administration of tafamidis (15, 30, and 45 mg/kg/day) from Gestation Day 7 through 17 resulted in decreased fetal weights at ≥30 mg/kg/day (approximately ≥9.7-times the human AUC at the clinical dose of 80 mg tafamidis meglumine). The no observable adverse effect level (NOAEL) for embryo-fetal development in rats was 15 mg/kg/day (6.6 times the human exposure of 80 mg tafamidis meglumine based on AUC).

In the rat pre- and postnatal development study with tafamidis, pregnant rats were orally administered tafamidis meglumine at doses of 5, 15, or 30 mg/kg/day from Gestation Day 7 through Lactation Day 20. High pup mortality at 30 mg/kg/day resulted in early termination of this group. Decreased pup survival and reduced pup weights was also noted at 15 mg/kg/day. Decreased pup weights in males were associated with delayed sexual maturation (preputial separation) at 15 mg/kg/day. Impaired performance in a water-maze test for learning and memory was observed at 15 mg/kg/day. The NOAEL for viability and growth in the F1 generation offspring following maternal dose administration during pregnancy and lactation with tafamidis was 5 mg/kg/day (human equivalent dose of tafamidis=0.8 mg/kg/day), a dose approximately equivalent to the clinical dose of 80 mg tafamidis meglumine.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

VYNDAQEL
Tafamidis meglumine capsules

Read this carefully before you start taking **VYNDAQEL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VYNDAQEL**.

What is VYNDAQEL used for?
VYNDAQEL is a prescription medicine used to treat adults with cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) to reduce death and hospitalization related to heart problems.

VYNDAQEL is not for use in patients less than 18 years of age.

How does VYNDAQEL work?
VYNDAQEL is used to treat a disease called transthyretin amyloidosis cardiomyopathy (also known as ATTR-CM). In ATTR-CM, a protein called transthyretin (TTR) breaks up and may form fibrils called amyloid. Amyloid can build up between cells in your heart preventing your heart from working normally. This can cause heart-related symptoms and problems. VYNDAQEL is used to prevent the TTR protein from breaking up and slows the deposit of amyloid fibrils in the heart.

What are the ingredients in VYNDAQEL?
Medicinal ingredients: tafamidis meglumine
Non-medicinal ingredients: ammonium hydroxide 28%, brilliant blue FCF, carmine, gelatin, glycerin, iron oxide (yellow), polyethylene glycol 400, polysorbate 80, polyvinyl acetate phthalate, propylene glycol, sorbitan monooleate, sorbitol, and titanium dioxide

VYNDAQEL comes in the following dosage form:
Capsules: 20 mg

Do not use VYNDAQEL if:
- You are allergic to tafamidis meglumine or any of the ingredients in this medicine

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VYNDAQEL. Talk about any health conditions or problems you may have, including if you:
- have liver problems.
- have severe kidney problems.
- had an organ transplant.
- are pregnant or plan to become pregnant. VYNDAQEL may harm your unborn baby. Tell your healthcare professional right away if you become pregnant or think you may be pregnant during treatment with VYNDAQEL. If you are a woman of childbearing potential, you should use appropriate contraception during treatment with VYNDAQEL and for one month after stopping treatment.

- are breastfeeding or plan to breastfeed. It is not known if VYNDAQEL passes into breast milk. You should not breastfeed during treatment with VYNDAQEL. Talk to your healthcare professional about the best way to feed your baby during treatment with VYNDAQEL.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VYNDAQEL:
- midazolam and triazolam, sedative drugs.
- methotrexate and imatinib, drugs used to treat cancer.
- rosuvastatin and pravastatin, drugs used to lower cholesterol.
- olmesartan, used to treat high blood pressure.
- acetylsalicylic acid, ibuprofen, naproxen, and other non-steroidal anti-inflammatory drugs.
- drugs used to treat HIV/AIDS.
- diuretics or water pills, used to treat high blood pressure.

How to take VYNDAQEL:
Take VYNDAQEL exactly as your healthcare professional tells you to.
VYNDAQEL capsule(s) should be swallowed whole and not crushed or cut.

Usual dose:
Take four (4) VYNDAQEL 20 mg capsules (for a total of 80 mg of VYNDAQEL) once a day, with or without food.
Your dose may be reduced to 20 mg once a day if you can't tolerate the usual dose.

Overdose:

If you think you have taken too much VYNDAQEL, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at your regularly scheduled time. Do not take 2 doses at the same time.

What are possible side effects from using VYNDAQEL?

These are not all the possible side effects you may feel when taking VYNDAQEL. If you experience any side effects not listed here, contact your healthcare professional.

- fall
- congested nose
- feeling weak or a lack of energy
- feeling unbalanced when standing or walking
- cataract (clouding of the lens in your eye)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Common			
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning sensation when passing urine.		x	

If you have a troublesome symptom or side effect that becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (15 to 25ºC).
- Keep out of reach and sight of children.

If you want more information about VYNDAQEL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (www.pfizer.ca), or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC

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