ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Health care professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 20 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 20 mg of micronized tafamidis meglumine equivalent to 12.2 mg tafamidis.

Excipient with known effect

Each soft capsule contains no more than 44 mg of sorbitol (E 420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

Yellow, opaque, oblong (approximately 21 mm) capsule imprinted with “VYN 20” in red.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vyndaqel is indicated for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician knowledgeable in the management of patients with transthyretin amyloid polyneuropathy (ATTR-PN).

Posology

The recommended dose of tafamidis meglumine is 20 mg orally once daily.

Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis.

If vomiting occurs after dosing, and the intact Vyndaqel capsule is identified, then an additional dose of Vyndaqel should be administered if possible. If no capsule is identified, then no additional dose is necessary, with resumption of dosing the next day as usual.

Special populations

Elderly

No dosage adjustment is required for elderly patients (≥ 65 years) (see section 5.2).

Hepatic and renal impairment

No dosage adjustment is required for patients with renal or mild and moderate hepatic impairment. Limited data are available in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min). Tafamidis meglumine has not been studied in patients with severe hepatic impairment and caution is recommended (see section 5.2).

Paediatric population

There is no relevant use of tafamidis in the paediatric population.

Method of administration

Oral use.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Women of childbearing potential should use appropriate contraception when taking tafamidis meglumine and continue to use appropriate contraception for 1-month after stopping treatment with tafamidis meglumine (see section 4.6).

Tafamidis meglumine should be added to the standard of care for the treatment of patients with ATTR-PN. Physicians should monitor patients and continue to assess the need for other therapy, including the need for liver transplantation, as part of this standard of care. As there are no data available regarding the use of tafamidis meglumine post-liver transplantation, tafamidis meglumine should be discontinued in patients who undergo liver transplantation.

Co-administration of tafamidis meglumine with substrates of the breast cancer resistant protein (BCRP) may increase exposure to the BCRP substrate. In case of co-administration, patients should be monitored for BCRP substrate related adverse reactions, and dose reduction of the BCRP substrate may be considered (see section 4.5).

This medicinal product contains no more than 44 mg sorbitol in each capsule. Sorbitol is a source of fructose.

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

In a clinical study in healthy volunteers, 20 mg tafamidis meglumine did not induce or inhibit the cytochrome P450 enzyme CYP3A4.

In vitro tafamidis inhibits the efflux transporter BCRP with IC50=1.16 µM and may cause drug-drug interactions at clinically relevant concentrations with substrates of this transporter (e.g. methotrexate, rosuvastatin, atorvastatin, apixaban, rivaroxaban, imatinib). In a clinical study in healthy participants, the exposure of the BCRP substrate rosuvastatin increased approximately 2-fold following multiple

daily doses of 61 mg tafamidis. Therefore, patients should be monitored for BCRP substrate related adverse reactions when used concomitantly with tafamidis. A dose reduction of the BCRP substrate may be considered (see section 4.4).

Likewise, tafamidis inhibits the uptake transporters OAT1 and OAT3 (organic anion transporters) with IC50=2.9 µM and IC50=2.36 µM, respectively, and may cause drug-drug interactions at clinically relevant concentrations with substrates of these transporters (e.g. non-steroidal anti-inflammatory drugs, bumetanide, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine). Based on *in vitro* data, the maximal predicted changes in AUC of OAT1 and OAT3 substrates were determined to be less than 1.25 for the tafamidis meglumine 20 mg dose, therefore, inhibition of OAT1 or OAT3 transporters by tafamidis is not expected to result in clinically significant interactions.

No interaction studies have been performed evaluating the effect of other medicinal products on tafamidis meglumine.

Laboratory test abnormality

Tafamidis may decrease serum concentrations of total thyroxine, without an accompanying change in free thyroxine (T4) or thyroid stimulating hormone (TSH). This observation in total thyroxine values may likely be the result of reduced thyroxine binding to or displacement from transthyretin (TTR) due to the high binding affinity tafamidis has to the TTR thyroxine receptor. No corresponding clinical findings consistent with thyroid dysfunction have been observed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Contraceptive measures should be used by women of childbearing potential during treatment with tafamidis meglumine, and for one month after stopping treatment, due to the prolonged half-life.

Pregnancy

There are no data on the use of tafamidis meglumine in pregnant women. Studies in animals have shown developmental toxicity (see section 5.3). Tafamidis meglumine is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Available data in animals have shown excretion of tafamidis in milk. A risk to the newborns/infants cannot be excluded. Tafamidis meglumine should not be used during breast-feeding.

Fertility

No impairment of fertility has been observed in nonclinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile, tafamidis meglumine is believed to have no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The overall clinical data reflect exposure of 127 patients with ATTR-PN to 20 mg of tafamidis meglumine administered daily for an average of 538 days (ranging from 15 to 994 days). The adverse reactions were generally mild or moderate in severity.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA System Organ Class (SOC) and frequency categories using the standard convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), and Uncommon (≥ 1/1,000 to < 1/100). Within the frequency group, adverse reactions are presented in order of decreasing seriousness. Adverse reactions reported from the clinical programme in the tabular listing below reflect the rates at which they occurred in the Phase 3, double-blind, placebo-controlled study (Fx-005).

System Organ Class	**Very Common**
Infections and infestations	Urinary tract infection
Gastrointestinal disorders	Diarrhoea
	Upper abdominal pain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

There is minimal clinical experience with overdose. During clinical trials, two patients diagnosed with transthyretin amyloid cardiomyopathy (ATTR-CM) accidentally ingested a single tafamidis meglumine dose of 160 mg without the occurrence of any associated adverse events. The highest dose of tafamidis meglumine given to healthy volunteers in a clinical trial was 480 mg as a single dose. There was one reported treatment-related adverse event of mild hordeolum at this dose.

Management

In case of overdose, standard supportive measures should be instituted as required.

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code N07XX08

Mechanism of action

Tafamidis is a selective stabiliser of TTR. Tafamidis binds to TTR at the thyroxine binding sites, stabilising the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.

Pharmacodynamic effects

Transthyretin amyloidosis is a severely debilitating condition induced by the accumulation of various insoluble fibrillar proteins, or amyloid, within the tissues in amounts sufficient to impair normal function. The dissociation of the transthyretin tetramer to monomers is the rate-limiting step in the pathogenesis of transthyretin amyloidosis. The folded monomers undergo partial denaturation to produce alternatively folded monomeric amyloidogenic intermediates. These intermediates then misassemble into soluble oligomers, profilaments, filaments, and amyloid fibrils. Tafamidis binds with negative cooperativity to the two thyroxine binding sites on the native tetrameric form of transthyretin preventing dissociation into monomers. The inhibition of TTR tetramer dissociation forms the rationale for the use of tafamidis to slow disease progression in stage 1 ATTR-PN patients.

A TTR stabilisation assay was utilised as a pharmacodynamic marker and assessed the stability of the TTR tetramer.

Tafamidis stabilised both the wild-type TTR tetramer and the tetramers of 14 TTR variants tested clinically after once-daily dosing with tafamidis. Tafamidis also stabilised the TTR tetramer for 25 variants tested *ex vivo*, thus demonstrating TTR stabilisation of 40 amyloidogenic TTR genotypes.

Clinical efficacy and safety

The pivotal study of tafamidis meglumine in stage 1 ATTR-PN patients was an 18-month, multicentre, randomised, double-blind, placebo-controlled study. The study evaluated the safety and efficacy of once-daily 20 mg tafamidis meglumine in 128 patients with ATTR-PN with the Val30Met mutation and primarily stage 1 disease; 126 of the 128 patients did not routinely require assistance with ambulation. The primary outcome measures were the Neuropathy Impairment Score of the Lower Limb (NIS-LL – a physician assessment of the neurologic exam of the lower limbs) and the Norfolk Quality of Life - Diabetic Neuropathy (Norfolk QOL-DN – a patient reported outcome, total quality of life score [TQOL]). Other outcome measures included composite scores of large nerve fibre (nerve conduction, vibration threshold and heart rate response to deep breathing - HRDB) and small nerve fibre function (heat pain and cooling threshold and HRDB) and nutritional assessments utilizing the modified body mass index (mBMI – BMI multiplied by serum albumin in g/L). Eighty-six of the 91 patients completing the 18 month treatment period subsequently enrolled in an open-label extension study, where they all received once daily 20 mg tafamidis meglumine for an additional 12 months.

Following 18 months of treatment, more tafamidis meglumine-treated patients were NIS-LL Responders (change of less than 2 points on NIS-LL) Outcomes for the pre-specified analyses of the primary endpoints are provided in the following table:

Vyndaqel versus Placebo: NIS-LL and TQOL at Month 18 (Study Fx-005)		
	Placebo	**Vyndaqel**
Pre-specified ITT Analysis	**N=61**	**N=64**
NIS-LL Responders (% Patients)	29.5%	45.3%
Difference (Vyndaqel minus Placebo) 95% CI of Difference (p-value)	15.8% -0.9%, 32.5% (0.068)	
TQOL Change from Baseline LSMean (SE)	7.2 (2.36)	2.0 (2.31)
Difference in LSMeans (SE) 95% CI of Difference (p-value)	-5.2 (3.31) -11.8, 1.3 (0.116)	
Pre-specified Efficacy Evaluable Analysis	**N=42**	**N=45**
NIS-LL Responders (% Patients)	38.1%	60.0%
Difference (Vyndaqel minus Placebo) 95% CI of Difference (p-value)	21.9% 1.4%, 42.4% (0.041)	
TQOL Change from Baseline LSMean (SE)	8.9 (3.08)	0.1 (2.98)
Difference in LSMeans (SE) 95% CI of Difference (p-value)	-8.8 (4.32) -17.4, -0.2 (0.045)	

Vyndaqel versus Placebo: NIS-LL and TQOL at Month 18 (Study Fx-005)		
	Placebo	**Vyndaqel**
Pre-specified ITT Analysis	**N=61**	**N=64**

In the pre-specified ITT NIS-LL Responder analysis, patients who discontinued prior to the 18-month time point due to liver transplantation were categorized as non-responders. The pre-specified Efficacy Evaluable analysis used observed data for those patients who completed the 18 month treatment per protocol.

The secondary endpoints demonstrated that tafamidis meglumine treatment resulted in less deterioration of neurologic function and improved nutritional status (mBMI) compared with placebo, as shown in the following table.

Secondary Endpoints Changes from Baseline to Month 18 LSMean (Standard Error) (Intent-to-Treat Population) (Study Fx-005)				
	Placebo N=61	**Vyndaqel N=64**	**P-value**	**Vyndaqel % change relative to Placebo**
NIS-LL change from BL *LSMean (SE)*	5.8 (0.96)	2.8 (0.95)	0.027	-52%
Large Fibre change from BL *LSMean (SE)*	3.2 (0.63)	1.5 (0.62)	0.066	-53%
Small Fibre change from BL *LSMean (SE)*	1.6 (0.32)	0.3 (0.31)	0.005	-81%
mBMI change from BL *LSMean (SE)*	-33.8 (11.8)	39.3 (11.5)	< 0.0001	NA

mBMI was derived as the product of serum albumin and Body Mass Index.
Based on repeated measures analysis of variance with change from baseline as the dependent variable, an unstructured covariance matrix, treatment, month and treatment-by-month as fixed effects, and subject as a random effect in the model.
NA=not applicable.

In the open-label extension study, the rate of change in the NIS-LL during the 12 months of treatment was similar to that observed in those patients randomised and treated with tafamidis in the previous double blind 18 month period.

The effects of tafamidis have been assessed in patients with non-Val30Met ATTR-PN in a supportive open-label study in 21 patients and a post-marketing observational study in 39 patients. Based on the results of these studies, the mechanism of action of tafamidis and the results on TTR stabilisation, tafamidis meglumine is expected to be beneficial in patients with stage 1 ATTR-PN due to mutations other than Val30Met.

The effects of tafamidis have been assessed in a double-blind, placebo-controlled, randomised 3-arm study in 441 patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM). The primary analysis of pooled tafamidis meglumine (20 mg and 80 mg) versus placebo demonstrated a significant reduction (p=0.0006) in all-cause mortality and frequency of cardiovascular-related hospitalisations.

A supra-therapeutic, single, 400 mg oral dose of tafamidis solution in healthy volunteers demonstrated no prolongation of the QTc interval.

The European Medicines Agency has waived the obligation to submit the results of studies with tafamidis in all subsets of the paediatric population in transthyretin amyloidosis (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under ‘exceptional circumstances’. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

After oral administration of the soft capsule once daily, the maximum peak concentration (C_{max}) is achieved within a median time (t_{max}) of 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 tafamidis with or without food.

Distribution

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

The extent of tafamidis binding to plasma proteins has been evaluated using animal and human plasma. The affinity of tafamidis for TTR is greater than that for albumin. Therefore, in plasma, tafamidis is likely to bind preferentially to TTR despite the significantly higher concentration of albumin (600 µM) relative to TTR (3.6 µM).

Biotransformation and elimination

There is no explicit evidence of biliary excretion of tafamidis in humans. Based on preclinical data, it is suggested that tafamidis is metabolised by glucuronidation and excreted via the bile. This route of biotransformation is plausible in humans, as approximately 59% of the total administered dose is recovered in faeces, and approximately 22% recovered in urine. Based on population pharmacokinetic results, the apparent oral clearance of tafamidis meglumine is 0.228 L/h and the population mean half-life is approximately 49 hours.

Dose and time linearity

Exposure from once-daily dosing with tafamidis meglumine increased with increasing dose up to 480 mg single dose and multiple doses up to 80 mg/day. In general, increases were proportional or near proportional to dose and tafamidis clearance was stationary over time.

Pharmacokinetic parameters were similar after single and repeated administration of 20 mg tafamidis meglumine, indicating a lack of induction or inhibition of tafamidis metabolism.

Results of once-daily dosing with 15 mg to 60 mg oral solution tafamidis meglumine for 14 days demonstrated that steady-state was achieved by Day 14.

Special populations

Hepatic impairment

Pharmacokinetic data indicated decreased systemic exposure (approximately 40%) and increased total clearance (0.52 L/h versus 0.31 L/h) of tafamidis meglumine in patients with moderate hepatic impairment (Child-Pugh Score of 7-9 inclusive) compared to healthy subjects due to a higher unbound fraction of tafamidis. As patients with moderate hepatic impairment have lower TTR levels than healthy subjects, dosage adjustment is not necessary as the stoichiometry of tafamidis with its target protein TTR would be sufficient for stabilisation of the TTR tetramer. The exposure to tafamidis in patients with severe hepatic impairment is unknown.

Renal impairment

Tafamidis has not specifically been evaluated in a dedicated study of patients with renal impairment. The influence of creatinine clearance on tafamidis pharmacokinetics was evaluated in a population pharmacokinetic analysis in patients with creatinine clearance greater than 18 mL/min.

Pharmacokinetic estimates indicated no difference in apparent oral clearance of tafamidis in patients with creatinine clearance less than 80 mL/min compared to those with creatinine clearance greater than or equal to 80 mL/min. Dosage adjustment in patients with renal impairment is considered not necessary.

Elderly

Based on population pharmacokinetic results, subjects ≥ 65 years had an average 15% lower estimate of apparent oral clearance at steady-state compared to subjects less than 65 years old. However, the difference in clearance results in < 20% increases in mean C_{max} and AUC compared to younger subjects and is not clinically significant.

Pharmacokinetic/pharmacodynamic relationships

In vitro data indicated that tafamidis does not significantly inhibit cytochrome P450 enzymes CYP1A2, CYP3A4, CYP3A5, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Tafamidis is not expected to cause clinically relevant drug interaction due to induction of CYP1A2, CYP2B6 or CYP3A4.

In vitro studies suggest that it is unlikely tafamidis will cause drug interactions at clinically relevant concentrations with substrates of UDP glucuronosyltransferase (UGT) systemically. Tafamidis may inhibit intestinal activities of UGT1A1.

Tafamidis showed a low potential to inhibit Multi-Drug Resistant Protein (MDR1) (also known as P-glycoprotein; P-gp) systemically and in the gastrointestinal (GI) tract, organic cation transporter 2 (OCT2), multidrug and toxin extrusion transporter 1 (MATE1) and MATE2K, organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 at clinically relevant concentrations.

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, fertility and early embryonic development, genotoxicity and carcinogenic potential. In repeat-dose toxicity and the carcinogenicity studies, the liver appeared as a target organ for toxicity in the different species tested. Liver effects were seen at exposures approximately ≥ 2.5-times the human AUC at steady-state at the clinical dose of 20 mg tafamidis meglumine.

In a developmental toxicity study in rabbits, a slight increase in skeletal malformations and variations, abortions in few females, reduced embryo-foetal survival, and reduction in foetal weights were observed at exposures approximately ≥ 7.2 times the human AUC at steady-state at the clinical dose of 20 mg tafamidis meglumine.

In the rat pre- and postnatal development study with tafamidis, decreased pup survival and reduced pup weights were noted following maternal dose administration during pregnancy and lactation at doses of 15 and 30 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 = 0.8 mg/kg/day), a dose approximately 4.6 times the clinical dose of 20 mg tafamidis meglumine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell

Gelatine (E 441)
Glycerine (E 422)
Yellow iron oxide (E 172)
Sorbitan
Sorbitol (E 420)
Mannitol (E 421)
Titanium dioxide (E 171)
Purified water

Capsule contents

Macrogol 400 (E 1521)
Sorbitan monooleate (E 494)
Polysorbate 80 (E 433)

Printing ink (Opacode purple)

Ethyl alcohol
Isopropyl alcohol
Purified water
Macrogol 400 (E 1521)
Polyvinyl acetate phthalate
Propylene glycol (E 1520)
Carmine (E 120)
Brilliant Blue FCF (E 133)
Ammonium hydroxide (E 527) 28%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/PA/alu/PVC-alu perforated unit dose blisters.

Pack sizes: a pack of 30 x 1 soft capsules and a multipack containing 90 (3 packs of 30 x 1) soft capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/717/001
EU/1/11/717/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 November 2011
Date of latest renewal: 22 July 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: https://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 61 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 61 mg of micronized tafamidis.

Excipient with known effect

Each soft capsule contains no more than 44 mg of sorbitol (E 420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

Reddish brown, opaque, oblong (approximately 21 mm) capsule printed with "VYN 61" in white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vyndaqel is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician knowledgeable in the management of patients with amyloidosis or cardiomyopathy.

When there is a suspicion in patients presenting with specific medical history or signs of heart failure or cardiomyopathy, etiologic diagnosis must be done by a physician knowledgeable in the management of amyloidosis or cardiomyopathy to confirm ATTR-CM and exclude AL amyloidosis before starting tafamidis, using appropriate assessment tools such as: bone scintigraphy and blood/urine assessment, and/or histological assessment by biopsy, and transthyretin (TTR) genotyping to characterise as wild-type or hereditary.

Posology

The recommended dose is one capsule of Vyndaqel 61 mg (tafamidis) orally once daily (see section 5.1).

Vyndaqel 61 mg (tafamidis) corresponds to 80 mg tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis (see section 5.2).

Vyndaqel should be started as early as possible in the disease course when the clinical benefit on disease progression could be more evident. Conversely, when amyloid-related cardiac damage is more

advanced, such as in NYHA Class III, the decision to start or maintain treatment should be taken at the discretion of a physician knowledgeable in the management of patients with amyloidosis or cardiomyopathy (see section 5.1). There are limited clinical data in patients with NYHA Class IV.

If vomiting occurs after dosing, and the intact Vyndaqel capsule is identified, then an additional dose of Vyndaqel should be administered if possible. If no capsule is identified, then no additional dose is necessary, with resumption of dosing the next day as usual.

Special populations

Elderly

No dosage adjustment is required for elderly patients (≥ 65 years) (see section 5.2).

Hepatic and renal impairment

No dosage adjustment is required for patients with renal or mild and moderate hepatic impairment. Limited data are available in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min). Tafamidis has not been studied in patients with severe hepatic impairment and caution is recommended (see section 5.2).

Paediatric population

There is no relevant use of tafamidis in the paediatric population.

Method of administration

Oral use.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Women of childbearing potential should use appropriate contraception when taking tafamidis and continue to use appropriate contraception for 1-month after stopping treatment with tafamidis (see section 4.6).

Tafamidis should be added to the standard of care for the treatment of patients with transthyretin amyloidosis. Physicians should monitor patients and continue to assess the need for other therapy, including the need for organ transplantation, as part of this standard of care. As there are no data available regarding the use of tafamidis in organ transplantation, tafamidis should be discontinued in patients who undergo organ transplantation.

Increase in liver function tests and decrease in thyroxine may occur (see section 4.5 and 4.8).

Co-administration of tafamidis with substrates of the breast cancer resistant protein (BCRP) may increase exposure to the BCRP substrate. In case of co-administration, patients should be monitored for BCRP substrate related adverse reactions, and dose reduction of the BCRP substrate may be considered (see section 4.5).

This medicinal product contains no more than 44 mg sorbitol in each capsule. Sorbitol is a source of fructose.

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

In a clinical study in healthy volunteers, 20 mg tafamidis meglumine did not induce or inhibit the cytochrome P450 enzyme CYP3A4.

In vitro tafamidis inhibits the efflux transporter BCRP at the 61 mg/day tafamidis dose with IC50=1.16 µM and may cause drug-drug interactions at clinically relevant concentrations with substrates of this transporter (e.g. methotrexate, rosuvastatin, atorvastatin, apixaban, rivaroxaban, imatinib). In a clinical study in healthy participants, the exposure of the BCRP substrate rosuvastatin increased approximately 2-fold following multiple daily doses of 61 mg tafamidis. Therefore, patients should be monitored for BCRP substrate related adverse reactions when used concomitantly with tafamidis. A dose reduction of the BCRP substrate may be considered (see section 4.4).

Likewise, tafamidis inhibits the uptake transporters OAT1 and OAT3 (organic anion transporters) with IC50=2.9 µM and IC50=2.36 µM, respectively, and may cause drug-drug interactions at clinically relevant concentrations with substrates of these transporters (e.g. non-steroidal anti-inflammatory drugs, bumetanide, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine). Based on *in vitro* data, the maximal predicted changes in AUC of OAT1 and OAT3 substrates were determined to be less than 1.25 for the tafamidis 61 mg dose, therefore, inhibition of OAT1 or OAT3 transporters by tafamidis is not expected to result in clinically significant interactions.

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

Laboratory test abnormality

Tafamidis may decrease serum concentrations of total thyroxine, without an accompanying change in free thyroxine (T4) or thyroid stimulating hormone (TSH). This observation in total thyroxine values may likely be the result of reduced thyroxine binding to or displacement from TTR due to the high binding affinity tafamidis has to the TTR thyroxine receptor. No corresponding clinical findings consistent with thyroid dysfunction have been observed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Contraceptive measures should be used by women of childbearing potential during treatment with tafamidis, and for one month after stopping treatment, due to the prolonged half-life.

Pregnancy

There are no data on the use of tafamidis in pregnant women. Studies in animals have shown developmental toxicity (see section 5.3). Tafamidis is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Available data in animals have shown excretion of tafamidis in milk. A risk to the newborns/infants cannot be excluded. Tafamidis should not be used during breast-feeding.

Fertility

No impairment of fertility has been observed in nonclinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile, tafamidis is believed to have no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety data reflect exposure of 176 patients with ATTR-CM to 80 mg (administered as 4 x 20 mg) of tafamidis meglumine administered daily in a 30-month placebo-controlled trial in patients diagnosed with ATTR-CM (see section 5.1).

The frequency of adverse events in patients treated with 80 mg tafamidis meglumine was generally similar and comparable to placebo.

The following adverse events were reported more often in patients treated with tafamidis meglumine 80 mg compared to placebo: flatulence [8 patients (4.5%) versus 3 patients (1.7%)] and liver function test increased [6 patients (3.4%) versus 2 patients (1.1%)]. A causal relationship has not been established.

Safety data for tafamidis 61 mg are available from its open-label long-term extension study.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA System Organ Class (SOC) and frequency categories using the standard convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), and Uncommon (≥ 1/1,000 to < 1/100). Within the frequency group, adverse reactions are presented in order of decreasing seriousness. Adverse reactions listed in the table below are from cumulative clinical data in ATTR-CM participants.

System Organ Class	Common
Gastrointestinal disorders	Diarrhoea
Skin and subcutaneous tissue disorders	Rash Pruritus

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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 the occurrence of any associated adverse events. The highest dose of tafamidis meglumine given to healthy volunteers in a clinical trial was 480 mg as a single dose. There was one reported treatment-related adverse event of mild hordeolum at this dose.

Management

In case of overdose, standard supportive measures should be instituted as required.

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX08

Mechanism of action

Tafamidis is a selective stabiliser of TTR. Tafamidis binds to TTR at the thyroxine binding sites, stabilising the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.

Pharmacodynamic effects

Transthyretin amyloidosis is a severely debilitating condition induced by the accumulation of various insoluble fibrillar proteins, or amyloid, within the tissues in amounts sufficient to impair normal function. The dissociation of the transthyretin tetramer to monomers is the rate-limiting step in the pathogenesis of transthyretin amyloidosis. The folded monomers undergo partial denaturation to produce alternatively folded monomeric amyloidogenic intermediates. These intermediates then misassemble into soluble oligomers, profilaments, filaments, and amyloid fibrils. Tafamidis binds with negative cooperativity to the two thyroxine binding sites on the native tetrameric form of transthyretin preventing dissociation into monomers. The inhibition of TTR tetramer dissociation forms the rationale for the use of tafamidis in ATTR-CM patients.

A TTR stabilisation assay was utilised as a pharmacodynamic marker, and assessed the stability of the TTR tetramer.

Tafamidis stabilised both the wild-type TTR tetramer and the tetramers of 14 TTR variants tested clinically after once-daily dosing with tafamidis. Tafamidis also stabilised the TTR tetramer for 25 variants tested *ex vivo*, thus demonstrating TTR stabilisation of 40 amyloidogenic TTR genotypes.

In a multicentre, international, double-blind, placebo-controlled, randomised study (see Clinical efficacy and safety section), TTR stabilisation was observed at Month 1 and was maintained through Month 30.

Biomarkers associated with heart failure (NT-proBNP and Troponin I) favoured Vyndaqel over placebo.

Clinical efficacy and safety

Efficacy was demonstrated in a multicentre, international, double-blind, placebo-controlled, randomised 3-arm study in 441 patients with wild-type or hereditary ATTR-CM.

Patients were randomised 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 as well as by baseline severity of disease (NYHA Class). Table 1 describes the patient demographics and baseline characteristics.

Table 1: 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)
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 hospitalisations, which is defined as the number of times a subject is hospitalised (i.e., admitted to a hospital) for cardiovascular-related morbidity. The method compared each patient to every other patient within each stratum in a pair-wise manner that proceeds in a hierarchical fashion using all-cause mortality followed by frequency of cardiovascular-related hospitalisations 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 hospitalisations in the pooled tafamidis 20 mg and 80 mg dose group versus placebo (Table 2).

Table 2: Primary analysis using Finkelstein-Schoenfeld (F-S) Method of all-cause mortality and frequency of cardiovascular-related hospitalisations

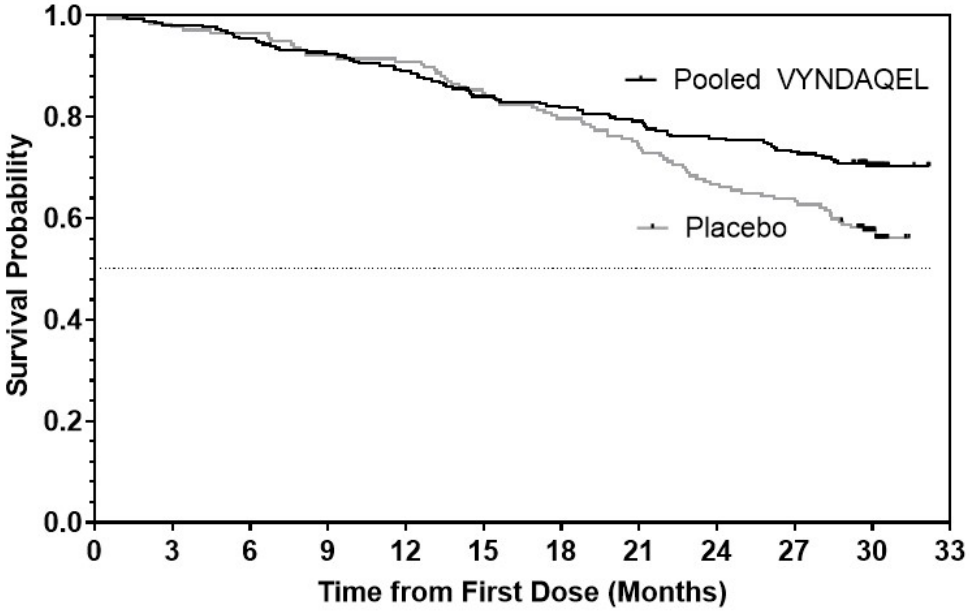
Primary analysis	Pooled Tafamidis N=264	Placebo N=177
Number (%) of subjects alive* at month 30	186 (70.5)	101 (57.1)
Average cardiovascular-related hospitalisations during 30 months (per patient per year) among those alive at month 30†	0.297	0.455
p-value from F-S Method	0.0006	

* 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.
† Descriptive mean among those who survived the 30 months.

Analysis of the individual components of the primary analysis (all-cause mortality and cardiovascular-related hospitalisation) also demonstrated significant reductions for tafamidis versus placebo.

The hazard ratio from the all-cause mortality Cox-proportional hazard model for pooled tafamidis was 0.698 (95% CI 0.508, 0.958), indicating a 30.2% reduction in the risk of death relative to the placebo group (p=0.0259). 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	78	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 New York Heart Association (NYHA) Baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors.

There were significantly fewer cardiovascular-related hospitalisations with tafamidis compared with placebo with a reduction in risk of 32.4% (Table 3).

Table 3: Cardiovascular-related hospitalisation frequency

	Pooled Tafamidis N=264	**Placebo N=177**
Total (%) number of subjects with Cardiovascular-related hospitalisations	138 (52.3)	107 (60.5)
Cardiovascular-related hospitalisations per year*	0.4750	0.7025
Pooled tafamidis versus placebo treatment difference (relative risk ratio)*	0.6761	
p-value*	< 0.0001	

Abbreviation: NYHA=New York Heart Association.
* 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 (composed of the Total Symptom, Physical Limitation, Quality of Life, and Social Limitation domains), respectively. A significant treatment effect favouring tafamidis was first observed at Month 6 and remained consistent through Month 30 on both the 6MWT distance and KCCQ-OS score (Table 4).

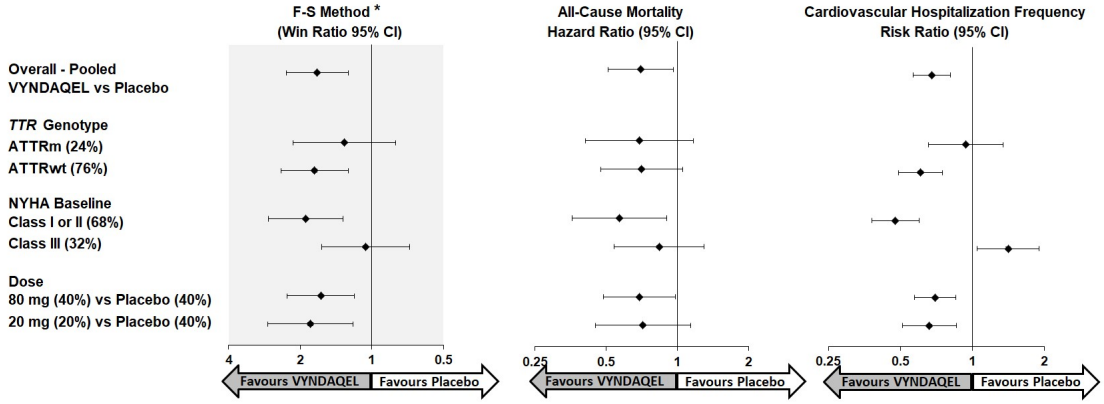
Table 4: 6MWT and KCCQ-OS and component domain scores

Endpoints	Baseline Mean (SD)		Change from Baseline to Month 30, LS mean (SE)		Treatment difference from placebo LS mean (95% CI)	*p-value*
	Pooled Tafamidis N=264	Placebo N=177	Pooled Tafamidis	Placebo		
6MWT* (metres)	350.55 (121.30)	353.26 (125.98)	-54.87 (5.07)	-130.55 (9.80)	75.68 (57.56, 93.80)	$p < 0.0001$
KCCQ-OS*	67.27 (21.36)	65.90 (21.74)	-7.16 (1.42)	-20.81 (1.97)	13.65 (9.48, 17.83)	$p < 0.0001$

* Higher values indicate better health status.
Abbreviations: 6MWT=6-Minute Walk Test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS=least squares; CI=confidence interval.

Results from F-S method represented by win ratio for the combined endpoint and its components (all-cause mortality and frequency of cardiovascular-related hospitalisation) consistently favoured tafamidis versus placebo by dose and across all subgroups (wild-type, variant and NYHA Class I & II, and III) except for cardiovascular-related hospitalisation frequency in NYHA Class III (Figure 2) which is higher in the tafamidis treated group compared to placebo (see section 4.2). Analyses of 6MWT and KCCQ-OS also favoured tafamidis relative to placebo within each subgroup.

Figure 2: Results from F-S Method and components by subgroup and dose



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 hospitalisation). The 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.

In applying the F-S method to each dose group individually, tafamidis reduced the combination of all-cause mortality and frequency of cardiovascular-related hospitalisations for both the 80 mg and 20 mg doses compared to placebo (p=0.0030 and p=0.0048, respectively). Results of the primary analysis, 6MWT at Month 30 and KCCQ-OS at Month 30 were statistically significant for both the tafamidis meglumine 80 mg and 20 mg doses versus placebo, with similar results for both doses.

Efficacy data for tafamidis 61 mg are not available as this formulation was not evaluated in the double-blind, placebo-controlled, randomised phase 3 study. The relative bioavailability of tafamidis 61 mg is similar to tafamidis meglumine 80 mg at steady-state (see section 5.2).

A supra-therapeutic, single, 400 mg oral dose of tafamidis meglumine solution in healthy volunteers demonstrated no prolongation of the QTc interval.

The European Medicines Agency has waived the obligation to submit the results of studies with tafamidis in all subsets of the paediatric population in transthyretin amyloidosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After oral administration of the soft capsule once daily, the maximum peak concentration (C_{max}) is achieved within a median time (t_{max}) of 4 hours for tafamidis 61 mg and 2 hours for tafamidis meglumine 80 mg (4 x 20 mg) 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 tafamidis with or without food.

Distribution

Tafamidis is highly protein bound (> 99%) in plasma. The apparent steady-state volume of distribution is 18.5 litres.

The extent of tafamidis binding to plasma proteins has been evaluated using animal and human plasma. The affinity of tafamidis for TTR is greater than that for albumin. Therefore, in plasma, tafamidis is likely to bind preferentially to TTR despite the significantly higher concentration of albumin (600 µM) relative to TTR (3.6 µM).

Biotransformation and elimination

There is no explicit evidence of biliary excretion of tafamidis in humans. Based on preclinical data, it is suggested that tafamidis is metabolised by glucuronidation and excreted via the bile. This route of biotransformation is plausible in humans, as approximately 59% of the total administered dose is recovered in faeces, and approximately 22% recovered in urine. Based on population pharmacokinetic results, the apparent oral clearance of tafamidis is 0.263 L/h and the population mean half-life is approximately 49 hours.

Dose and time linearity

Exposure from once-daily dosing with tafamidis meglumine increased with increasing dose up to 480 mg single dose and multiple doses up to 80 mg/day. In general, increases were proportional or near proportional to dose and tafamidis clearance was stationary over time.

The relative bioavailability of tafamidis 61 mg is similar to tafamidis meglumine 80 mg at steady-state. Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis.

Pharmacokinetic parameters were similar after single and repeated administration of 20 mg dose of tafamidis meglumine, indicating a lack of induction or inhibition of tafamidis metabolism.

Results of once-daily dosing with 15 mg to 60 mg oral solution tafamidis meglumine for 14 days demonstrated that steady-state was achieved by Day 14.

Special populations

Hepatic impairment

Pharmacokinetic data indicated decreased systemic exposure (approximately 40%) and increased total clearance (0.52 L/h versus 0.31 L/h) of tafamidis meglumine in patients with moderate hepatic impairment (Child-Pugh Score of 7-9 inclusive) compared to healthy subjects due to a higher unbound fraction of tafamidis. As patients with moderate hepatic impairment have lower TTR levels than healthy subjects, dosage adjustment is not necessary as the stoichiometry of tafamidis with its target protein TTR would be sufficient for stabilisation of the TTR tetramer. The exposure to tafamidis in patients with severe hepatic impairment is unknown.

Renal impairment

Tafamidis has not specifically been evaluated in a dedicated study of patients with renal impairment. The influence of creatinine clearance on tafamidis pharmacokinetics was evaluated in a population pharmacokinetic analysis in patients with creatinine clearance greater than 18 mL/min. Pharmacokinetic estimates indicated no difference in apparent oral clearance of tafamidis in patients with creatinine clearance less than 80 mL/min compared to those with creatinine clearance greater than or equal to 80 mL/min. Dosage adjustment in patients with renal impairment is considered not necessary.

Elderly

Based on population pharmacokinetic results, subjects ≥ 65 years had an average 15% lower estimate of apparent oral clearance at steady-state compared to subjects less than 65 years old. However, the difference in clearance results in < 20% increases in mean C_{max} and AUC compared to younger subjects and is not clinically significant.

Pharmacokinetic/pharmacodynamic relationships

In vitro data indicated that tafamidis does not significantly inhibit cytochrome P450 enzymes CYP1A2, CYP3A4, CYP3A5, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Tafamidis is not expected to cause clinically relevant drug interaction due to induction of CYP1A2, CYP2B6 or CYP3A4.

In vitro studies suggest that it is unlikely tafamidis will cause drug interactions at clinically relevant concentrations with substrates of UDP glucuronosyltransferase (UGT) systemically. Tafamidis may inhibit intestinal activities of UGT1A1.

Tafamidis showed a low potential to inhibit Multi-Drug Resistant Protein (MDR1) (also known as P-glycoprotein; P-gp) systemically and in the gastrointestinal (GI) tract, organic cation transporter 2 (OCT2), multidrug and toxin extrusion transporter 1 (MATE1) and MATE2K, organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 at clinically relevant concentrations.

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, fertility and early embryonic development, genotoxicity, and carcinogenic potential. In repeat-dose toxicity and the carcinogenicity studies, the liver appeared as a target organ for toxicity in the different species tested. Liver effects were seen at exposures approximately equal to the human AUC at steady-state at the clinical dose of 61 mg tafamidis.

In a developmental toxicity study in rabbits, a slight increase in skeletal malformations and variations, abortions in few females, reduced embryo-foetal survival, and reduction in foetal weights were observed at exposures approximately ≥ 2.1 times the human AUC at steady-state at the clinical dose of 61 mg tafamidis.

In the rat pre- and postnatal development study with tafamidis, decreased pup survival and reduced pup weights were noted following maternal dose administration during pregnancy and lactation at doses of 15 and 30 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 equal to the clinical dose of 61 mg tafamidis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell

Gelatine (E 441)
Glycerine (E 422)
Red iron oxide (E 172)
Sorbitan
Sorbitol (E 420)
Mannitol (E 421)
Purified water

Capsule contents

Macrogol 400 (E 1521)
Polysorbate 20 (E 432)
Povidone (K-value 90)
Butylated hydroxytoluene (E 321)

Printing ink (Opacode white)

Ethyl alcohol
Isopropyl alcohol
Purified water
Macrogol 400 (E 1521)
Polyvinyl acetate phthalate
Propylene glycol (E 1520)
Titanium dioxide (E 171)
Ammonium hydroxide (E 527) 28%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

PVC/PA/alu/PVC-alu perforated unit dose blisters.

Pack sizes: a pack of 30 x 1 soft capsules and a multipack containing 90 (3 packs of 30 x 1) soft capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/717/003
EU/1/11/717/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 November 2011
Date of latest renewal: 22 July 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: https://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 61 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 61 mg of micronized tafamidis.

Excipient with known effect

Each tablet contains 139.63 mg of lactose monohydrate (E 24).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Round white to off-white film-coated tablet embossed with “61” on one side. The tablet is 11 mm round.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vyndaqel is indicated for the treatment of wild-type transthyretin amyloidosis in adult patients with cardiomyopathy (ATTRwt-CM).

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician knowledgeable in the management of patients with amyloidosis or cardiomyopathy.

When there is a suspicion in patients presenting with specific medical history or signs of heart failure or cardiomyopathy, etiologic diagnosis must be done by a physician knowledgeable in the management of amyloidosis or cardiomyopathy to confirm ATTR-CM and exclude AL amyloidosis before starting tafamidis, using appropriate assessment tools such as: bone scintigraphy and blood/urine assessment, and/or histological assessment by biopsy, and transthyretin (TTR) genotyping to characterise as wild-type or hereditary.

Posology

The recommended dose is one tablet of Vyndaqel 61 mg (tafamidis) orally once daily (see section 5.1).

Vyndaqel 61 mg (tafamidis) corresponds to 80 mg tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis (see section 5.2).

No dose adjustment is required when changing from Vyndaqel 61 mg soft capsule to Vyndaqel 61 mg film-coated tablet.

Vyndaqel should be started as early as possible in the disease course when the clinical benefit on disease progression could be more evident. Conversely, when amyloid-related cardiac damage is more advanced, such as in NYHA Class III, the decision to start or maintain treatment should be taken at the discretion of a physician knowledgeable in the management of patients with amyloidosis or cardiomyopathy (see section 5.1). There are limited clinical data in patients with NYHA Class IV.

If vomiting occurs after dosing, and the intact Vyndaqel tablet is identified, then an additional dose of Vyndaqel should be administered if possible. If no tablet is identified, then no additional dose is necessary, with resumption of dosing the next day as usual.

Special populations

Elderly

No dosage adjustment is required for elderly patients (≥ 65 years) (see section 5.2).

Hepatic and renal impairment

No dosage adjustment is required for patients with renal or mild and moderate hepatic impairment. Limited data are available in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min). Tafamidis has not been studied in patients with severe hepatic impairment and caution is recommended (see section 5.2).

Paediatric population

There is no relevant use of tafamidis in the paediatric population.

Method of administration

Oral use.

The film-coated tablets should be swallowed whole and not crushed or cut. Vyndaqel may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Women of childbearing potential should use appropriate contraception when taking tafamidis and continue to use appropriate contraception for one-month after stopping treatment with tafamidis (see section 4.6).

Tafamidis should be added to the standard of care for the treatment of patients with transthyretin amyloidosis. Physicians should monitor patients and continue to assess the need for other therapy, including the need for organ transplantation, as part of this standard of care. As there are no data available regarding the use of tafamidis in organ transplantation, tafamidis should be discontinued in patients who undergo organ transplantation.

Increase in liver function tests and decrease in thyroxine may occur (see section 4.5 and 4.8).

Co-administration of tafamidis with substrates of the breast cancer resistant protein (BCRP) may increase exposure to the BCRP substrate. In case of co-administration, patients should be monitored for BCRP substrate related adverse reactions, and dose reduction of the BCRP substrate may be considered (see section 4.5).

Excipients

Lactose monohydrate

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

In a clinical study in healthy volunteers, 20 mg tafamidis meglumine did not induce or inhibit the cytochrome P450 enzyme CYP3A4.

In vitro tafamidis inhibits the efflux transporter BCRP at the 61 mg/day tafamidis dose with IC50=1.16 µM and may cause drug-drug interactions at clinically relevant concentrations with substrates of this transporter (e.g. methotrexate, rosuvastatin, atorvastatin, apixaban, rivaroxaban, imatinib). In a clinical study in healthy participants, the exposure of the BCRP substrate rosuvastatin increased approximately 2-fold following multiple daily doses of 61 mg tafamidis. Therefore, patients should be monitored for BCRP substrate related adverse reactions when used concomitantly with tafamidis. A dose reduction of the BCRP substrate may be considered (see section 4.4).

Likewise, tafamidis inhibits the uptake transporters OAT1 and OAT3 (organic anion transporters) with IC50=2.9 µM and IC50=2.36 µM, respectively, and may cause drug-drug interactions at clinically relevant concentrations with substrates of these transporters (e.g. non-steroidal anti-inflammatory drugs, bumetanide, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine). Based on *in vitro* data, the maximal predicted changes in AUC of OAT1 and OAT3 substrates were determined to be less than 1.25 for the tafamidis 61 mg dose, therefore, inhibition of OAT1 or OAT3 transporters by tafamidis is not expected to result in clinically significant interactions.

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

Laboratory test abnormality

Tafamidis may decrease serum concentrations of total thyroxine, without an accompanying change in free thyroxine (T4) or thyroid stimulating hormone (TSH). This observation in total thyroxine values may likely be the result of reduced thyroxine binding to or displacement from TTR due to the high binding affinity tafamidis has to the TTR thyroxine receptor. No corresponding clinical findings consistent with thyroid dysfunction have been observed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Contraceptive measures should be used by women of childbearing potential during treatment with tafamidis, and for one month after stopping treatment, due to the prolonged half-life.

Pregnancy

There are no data on the use of tafamidis in pregnant women. Studies in animals have shown developmental toxicity (see section 5.3). Tafamidis is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Available data in animals have shown excretion of tafamidis in milk. A risk to the newborns/infants cannot be excluded. Tafamidis should not be used during breast-feeding.

Fertility

No impairment of fertility has been observed in nonclinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile, tafamidis is believed to have no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety data reflect exposure of 176 patients with ATTR-CM to 80 mg (administered as 4 x 20 mg) of tafamidis meglumine administered daily in a 30-month placebo-controlled trial in patients diagnosed with ATTR-CM (see section 5.1).

The frequency of adverse events in patients treated with 80 mg tafamidis meglumine was generally similar and comparable to placebo.

The following adverse events were reported more often in patients treated with tafamidis meglumine 80 mg compared to placebo: flatulence [8 patients (4.5%) versus 3 patients (1.7%)] and liver function test increased [6 patients (3.4%) versus 2 patients (1.1%)]. A causal relationship has not been established.

Safety data for tafamidis 61 mg are available from its open-label long-term extension study.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA System Organ Class (SOC) and frequency categories using the standard convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), and Uncommon (≥ 1/1,000 to < 1/100). Within the frequency group, adverse reactions are presented in order of decreasing seriousness. Adverse reactions listed in the table below are from cumulative clinical data in ATTR-CM participants.

System Organ Class	**Common**
Gastrointestinal disorders	Diarrhoea
Skin and subcutaneous tissue disorders	Rash Pruritus

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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 the occurrence of any associated adverse events. The highest dose of tafamidis meglumine given to healthy volunteers in a clinical trial was 480 mg as a single dose. There was one reported treatment-related adverse event of mild hordeolum at this dose.

Management

In case of overdose, standard supportive measures should be instituted as required.

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX08

Mechanism of action

Tafamidis is a selective stabiliser of TTR. Tafamidis binds to TTR at the thyroxine binding sites, stabilising the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.

Pharmacodynamic effects

Transthyretin amyloidosis is a severely debilitating condition induced by the accumulation of various insoluble fibrillar proteins, or amyloid, within the tissues in amounts sufficient to impair normal function. The dissociation of the transthyretin tetramer to monomers is the rate-limiting step in the pathogenesis of transthyretin amyloidosis. The folded monomers undergo partial denaturation to produce alternatively folded monomeric amyloidogenic intermediates. These intermediates then misassemble into soluble oligomers, profilaments, filaments, and amyloid fibrils. Tafamidis binds with negative cooperativity to the two thyroxine binding sites on the native tetrameric form of transthyretin preventing dissociation into monomers. The inhibition of TTR tetramer dissociation forms the rationale for the use of tafamidis in ATTR-CM patients.

A TTR stabilisation assay was utilised as a pharmacodynamic marker, and assessed the stability of the TTR tetramer.

Tafamidis stabilised both the wild-type TTR tetramer and the tetramers of 14 TTR variants tested clinically after once-daily dosing with tafamidis. Tafamidis also stabilised the TTR tetramer for 25 variants tested *ex vivo*, thus demonstrating TTR stabilisation of 40 amyloidogenic TTR genotypes.

In a multicentre, international, double-blind, placebo-controlled, randomised study (see Clinical efficacy and safety section), TTR stabilisation was observed at Month 1 and was maintained through Month 30.

Biomarkers associated with heart failure (NT-proBNP and Troponin I) favoured Vyndaqel over placebo.

Clinical efficacy and safety

Efficacy was demonstrated in a multicentre, international, double-blind, placebo-controlled, randomised 3-arm study in 441 patients with wild-type or hereditary ATTR-CM.

Patients were randomised 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 as well as by baseline severity of disease (NYHA Class). Table 1 describes the patient demographics and baseline characteristics.

Table 1: 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)
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 hospitalisations, which is defined as the number of times a subject is hospitalised (i.e., admitted to a hospital) for cardiovascular-related morbidity. The method compared each patient to every other patient within each stratum in a pair-wise manner that proceeds in a hierarchical fashion using all-cause mortality followed by frequency of cardiovascular-related hospitalisations 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 hospitalisations in the pooled tafamidis 20 mg and 80 mg dose group versus placebo (Table 2).

Table 2: Primary analysis using Finkelstein-Schoenfeld (F-S) Method of all-cause mortality and frequency of cardiovascular-related hospitalisations

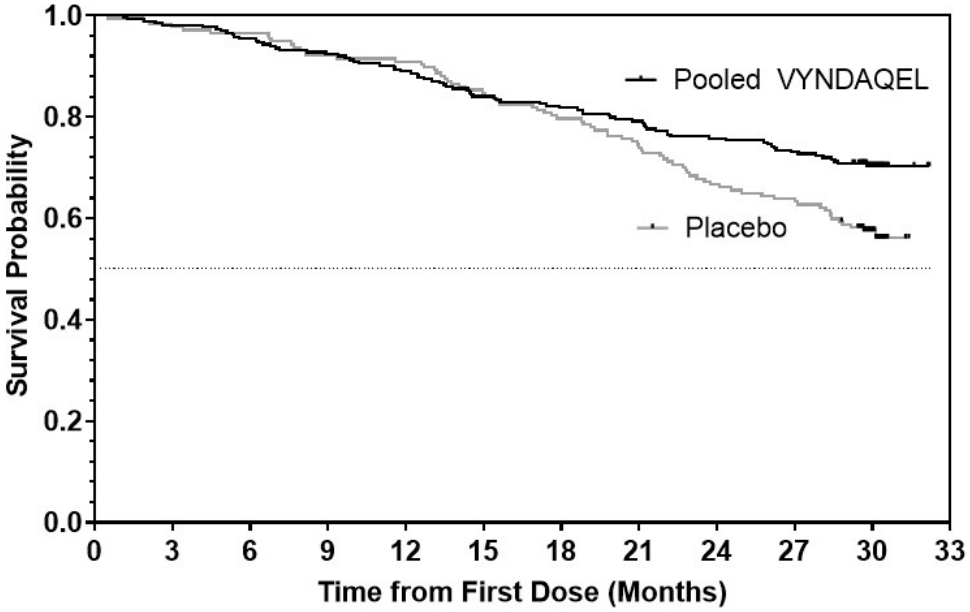
Primary analysis	**Pooled Tafamidis N=264**	**Placebo N=177**
Number (%) of subjects alive* at month 30	186 (70.5)	101 (57.1)
Average cardiovascular-related hospitalisations during 30 months (per patient per year) among those alive at month 30†	0.297	0.455
p-value from F-S Method	0.0006	

* 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.
† Descriptive mean among those who survived the 30 months.

Analysis of the individual components of the primary analysis (all-cause mortality and cardiovascular-related hospitalisation) also demonstrated significant reductions for tafamidis versus placebo.

The hazard ratio from the all-cause mortality Cox-proportional hazard model for pooled tafamidis was 0.698 (95% CI 0.508, 0.958), indicating a 30.2% reduction in the risk of death relative to the placebo group (p=0.0259). 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	78	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 New York Heart Association (NYHA) Baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors.

There were significantly fewer cardiovascular-related hospitalisations with tafamidis compared with placebo with a reduction in risk of 32.4% (Table 3).

Table 3: Cardiovascular-related hospitalisation frequency

	Pooled Tafamidis N=264	**Placebo N=177**
Total (%) number of subjects with Cardiovascular-related hospitalisations	138 (52.3)	107 (60.5)
Cardiovascular-related hospitalisations per year*	0.4750	0.7025
Pooled tafamidis versus placebo treatment difference (relative risk ratio)*	0.6761	
p-value*	< 0.0001	

Abbreviation: NYHA=New York Heart Association.
* 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 (composed of the Total Symptom, Physical Limitation, Quality of Life, and Social

Limitation domains), respectively. A significant treatment effect favouring tafamidis was first observed at Month 6 and remained consistent through Month 30 on both the 6MWT distance and KCCQ-OS score (Table 4).

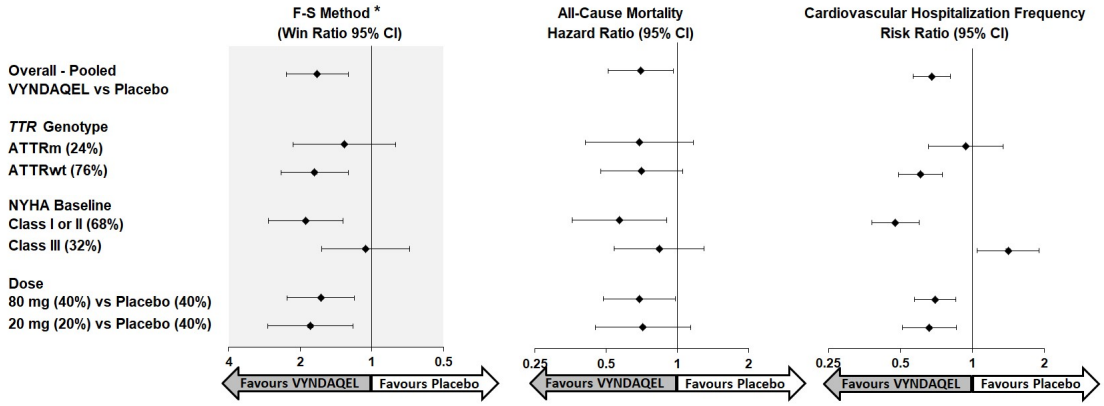
Table 4: 6MWT and KCCQ-OS and component domain scores

Endpoints	Baseline Mean (SD)		Change from Baseline to Month 30, LS mean (SE)		Treatment difference from placebo LS mean (95% CI)	*p-value*
	Pooled Tafamidis N=264	Placebo N=177	Pooled Tafamidis	Placebo		
6MWT* (metres)	350.55 (121.30)	353.26 (125.98)	-54.87 (5.07)	-130.55 (9.80)	75.68 (57.56, 93.80)	$p < 0.0001$
KCCQ-OS*	67.27 (21.36)	65.90 (21.74)	-7.16 (1.42)	-20.81 (1.97)	13.65 (9.48, 17.83)	$p < 0.0001$

* Higher values indicate better health status.
Abbreviations: 6MWT=6-Minute Walk Test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS=least squares; CI=confidence interval.

Results from F-S method represented by win ratio for the combined endpoint and its components (all-cause mortality and frequency of cardiovascular-related hospitalisation) consistently favoured tafamidis versus placebo by dose and across all subgroups (wild-type, variant and NYHA Class I & II, and III) except for cardiovascular-related hospitalisation frequency in NYHA Class III (Figure 2) which is higher in the tafamidis treated group compared to placebo (see section 4.2). Analyses of 6MWT and KCCQ-OS also favoured tafamidis relative to placebo within each subgroup.

Figure 2: Results from F-S Method and components by subgroup and dose



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 hospitalisation). The 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.

In applying the F-S method to each dose group individually, tafamidis reduced the combination of all-cause mortality and frequency of cardiovascular-related hospitalisations for both the 80 mg and 20 mg doses compared to placebo (p=0.0030 and p=0.0048, respectively). Results of the primary analysis, 6MWT at Month 30 and KCCQ-OS at Month 30 were statistically significant for both the tafamidis meglumine 80 mg and 20 mg doses versus placebo, with similar results for both doses.

Efficacy data for tafamidis 61 mg are not available as this formulation was not evaluated in the double-blind, placebo-controlled, randomised phase 3 study. The relative bioavailability of tafamidis 61 mg is similar to tafamidis meglumine 80 mg at steady-state (see section 5.2). The relative bioavailability of the 61 mg tablet is similar to the 61 mg capsule.

A supra-therapeutic, single, 400 mg oral dose of tafamidis meglumine solution in healthy volunteers demonstrated no prolongation of the QTc interval.

The European Medicines Agency has waived the obligation to submit the results of studies with tafamidis in all subsets of the paediatric population in transthyretin amyloidosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After oral administration of the film-coated tablet once daily, the maximum peak concentration (C_{max}) is achieved within a median time (t_{max}) of 4 hours for tafamidis 61 mg 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 tafamidis with or without food.

Distribution

Tafamidis is highly protein bound (> 99%) in plasma. The apparent steady-state volume of distribution is 18.5 litres.

The extent of tafamidis binding to plasma proteins has been evaluated using animal and human plasma. The affinity of tafamidis for TTR is greater than that for albumin. Therefore, in plasma, tafamidis is likely to bind preferentially to TTR despite the significantly higher concentration of albumin (600 µM) relative to TTR (3.6 µM).

Biotransformation and elimination

There is no explicit evidence of biliary excretion of tafamidis in humans. Based on preclinical data, it is suggested that tafamidis is metabolised by glucuronidation and excreted via the bile. This route of biotransformation is plausible in humans, as approximately 59% of the total administered dose is recovered in faeces, and approximately 22% recovered in urine. Based on population pharmacokinetic results, the apparent oral clearance of tafamidis is 0.263 L/h and the population mean half-life is approximately 49 hours.

Dose and time linearity

Exposure from once-daily dosing with tafamidis meglumine increased with increasing dose up to 480 mg single dose and multiple doses up to 80 mg/day. In general, increases were proportional or near proportional to dose and tafamidis clearance was stationary over time.

The relative bioavailability of tafamidis 61 mg is similar to tafamidis meglumine 80 mg at steady-state. Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis.

Pharmacokinetic parameters were similar after single and repeated administration of 20 mg dose of tafamidis meglumine, indicating a lack of induction or inhibition of tafamidis metabolism.

Results of once-daily dosing with 15 mg to 60 mg oral solution tafamidis meglumine for 14 days demonstrated that steady-state was achieved by Day 14.

Special populations

Hepatic impairment

Pharmacokinetic data indicated decreased systemic exposure (approximately 40%) and increased total clearance (0.52 L/h versus 0.31 L/h) of tafamidis meglumine in patients with moderate hepatic impairment (Child-Pugh Score of 7-9 inclusive) compared to healthy subjects due to a higher unbound

fraction of tafamidis. As patients with moderate hepatic impairment have lower TTR levels than healthy subjects, dosage adjustment is not necessary as the stoichiometry of tafamidis with its target protein TTR would be sufficient for stabilisation of the TTR tetramer. The exposure to tafamidis in patients with severe hepatic impairment is unknown.

Renal impairment

Tafamidis has not specifically been evaluated in a dedicated study of patients with renal impairment. The influence of creatinine clearance on tafamidis pharmacokinetics was evaluated in a population pharmacokinetic analysis in patients with creatinine clearance greater than 18 mL/min. Pharmacokinetic estimates indicated no difference in apparent oral clearance of tafamidis in patients with creatinine clearance less than 80 mL/min compared to those with creatinine clearance greater than or equal to 80 mL/min. Dosage adjustment in patients with renal impairment is considered not necessary.

Elderly

Based on population pharmacokinetic results, subjects ≥ 65 years had an average 15% lower estimate of apparent oral clearance at steady-state compared to subjects less than 65 years old. However, the difference in clearance results in < 20% increases in mean C_{max} and AUC compared to younger subjects and is not clinically significant.

Pharmacokinetic/pharmacodynamic relationships

In vitro data indicated that tafamidis does not significantly inhibit cytochrome P450 enzymes CYP1A2, CYP3A4, CYP3A5, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Tafamidis is not expected to cause clinically relevant drug interaction due to induction of CYP1A2, CYP2B6 or CYP3A4.

In vitro studies suggest that it is unlikely tafamidis will cause drug interactions at clinically relevant concentrations with substrates of UDP glucuronosyltransferase (UGT) systemically. Tafamidis may inhibit intestinal activities of UGT1A1.

Tafamidis showed a low potential to inhibit Multi-Drug Resistant Protein (MDR1) (also known as P-glycoprotein; P-gp) systemically and in the gastrointestinal (GI) tract, organic cation transporter 2 (OCT2), multidrug and toxin extrusion transporter 1 (MATE1) and MATE2K, organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 at clinically relevant concentrations.

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, fertility and early embryonic development, genotoxicity, and carcinogenic potential. In repeat-dose toxicity and the carcinogenicity studies, the liver appeared as a target organ for toxicity in the different species tested. Liver effects were seen at exposures approximately equal to the human AUC at steady-state at the clinical dose of 61 mg tafamidis.

In a developmental toxicity study in rabbits, a slight increase in skeletal malformations and variations, abortions in few females, reduced embryo-foetal survival, and reduction in foetal weights were observed at exposures approximately ≥ 2.1 times the human AUC at steady-state at the clinical dose of 61 mg tafamidis.

In the rat pre- and postnatal development study with tafamidis, decreased pup survival and reduced pup weights were noted following maternal dose administration during pregnancy and lactation at doses of 15 and 30 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 equal to the clinical dose of 61 mg tafamidis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E 460)
Lactose monohydrate (E 24)
Crospovidone (E 1202)
Magnesium stearate (E 470b)

Film coating (Opadry TF white)

Calcium carbonate
Isomalt
Hypromellose
Medium-chain triglycerides

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

OPA/Al/PVC-alu blisters

Pack sizes: a pack of 3 x 10 film-coated tablets and a pack of 9 x 10 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/717/005
EU/1/11/717/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 November 2011
Date of latest renewal: 22 July 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Vyndaqel 20 mg soft capsules and Vyndaqel 61 mg soft capsules
Pfizer Service Company BV
Hermeslaan 11
1932 Zaventem
Belgium

Or

Millmount Healthcare Limited
Block 7, City North Business Campus
Stamullen
K32 YD60
Ireland

Or

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79108 Freiburg Im Breisgau
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

Vyndaqel 61 mg film-coated tablets
Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79108 Freiburg Im Breisgau
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Vyndaqel (tafamidis) in each Member State, the MAH must agree on the content and format of the Healthcare Professional Guide, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The Healthcare Professional Guide is aimed at raising prescribers awareness around:

- The need to counsel patients on appropriate precautions when using tafamidis, particularly the avoidance of pregnancy and the need to use effective contraception methods.
- Advising female patients to inform their doctor immediately in case of exposure to tafamidis during (or within one month prior to) pregnancy for physicians' reporting and assessment.
- Joining the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) program in case of exposure to tafamidis during pregnancy to collect additional data on pregnancy outcome, birth, neonate/infant health and 12 month follow-up with milestones reached; details on how to report pregnancies for women receiving Vyndaqel (tafamidis) will be provided.
- Advising patients to contact their doctor about any adverse events while taking tafamidis and reminding physicians and pharmacists of the requirement to report suspected adverse reactions related to Vyndaqel (tafamidis).
- The clinical criteria for the diagnosis of ATTR-CM before prescribing tafamidis, to avoid administration to non-qualifying patients.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measure:

Description	Due date
The MAH shall provide yearly updates on any new information concerning the effects of Vyndaqel on disease progression and its long-term safety in non Val30Met patients.	Yearly, simultaneously with submission of Periodic Safety Update Reports. (when applicable)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

Pack of 30 x 1 soft capsules – WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 20 mg soft capsules
tafamidis meglumine

2. STATEMENT OF ACTIVE SUBSTANCES

Each soft capsule contains 20 mg micronized tafamidis meglumine equivalent to 12.2 mg tafamidis.

3. LIST OF EXCIPIENTS

The capsule contains sorbitol (E 420). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
To remove capsule: tear off one individual blister and push through the aluminium foil.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/717/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vyndaqel 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

Multipack of 90 (3 packs of 30 x 1) soft capsules – WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 20 mg soft capsules
tafamidis meglumine

2. STATEMENT OF ACTIVE SUBSTANCES

Each soft capsule contains 20 mg micronized tafamidis meglumine equivalent to 12.2 mg tafamidis.

3. LIST OF EXCIPIENTS

The capsule contains sorbitol (E 420). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 90 (3 packs of 30 x 1) soft capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
To remove capsule: tear off one individual blister and push through the aluminium foil.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/717/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vyndaqel 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON

Pack of 30 – for multipack of 90 (3 packs of 30 x 1) soft capsules – WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 20 mg soft capsules
tafamidis meglumine

2. STATEMENT OF ACTIVE SUBSTANCES

Each soft capsule contains 20 mg micronized tafamidis meglumine equivalent to 12.2 mg tafamidis.

3. LIST OF EXCIPIENTS

The capsule contains sorbitol (E 420). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 soft capsules. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
To remove capsule: tear off one individual blister and push through the aluminium foil.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/717/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vyndaqel 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

Perforated unit dose blisters of 10 x 20 mg Vyndaqel soft capsules

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 20 mg soft capsules
tafamidis meglumine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

Pack of 30 x 1 soft capsules – WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 61 mg soft capsules
tafamidis

2. STATEMENT OF ACTIVE SUBSTANCES

Each soft capsule contains 61 mg micronized tafamidis.

3. LIST OF EXCIPIENTS

The capsule contains sorbitol (E 420). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
To remove capsule: tear off one individual blister and push through the aluminium foil.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/717/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vyndaqel 61 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

Multipack of 90 (3 packs of 30 x 1) soft capsules – WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 61 mg soft capsules
tafamidis

2. STATEMENT OF ACTIVE SUBSTANCES

Each soft capsule contains 61 mg micronized tafamidis.

3. LIST OF EXCIPIENTS

The capsule contains sorbitol (E 420). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 90 (3 packs of 30 x 1) soft capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
To remove capsule: tear off one individual blister and push through the aluminium foil.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/717/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vyndaqel 61 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON

Pack of 30 – for multipack of 90 (3 packs of 30 x 1) soft capsules – WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 61 mg soft capsules
tafamidis

2. STATEMENT OF ACTIVE SUBSTANCES

Each soft capsule contains 61 mg micronized tafamidis.

3. LIST OF EXCIPIENTS

The capsule contains sorbitol (E 420). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 soft capsules. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
To remove capsule: tear off one individual blister and push through the aluminium foil.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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EU/1/11/717/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vyndaqel 61 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

Perforated unit dose blisters of 10 x 61 mg Vyndaqel soft capsules

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 61 mg soft capsules
tafamidis

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 61 MG BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 61 mg film-coated tablets
tafamidis

2. STATEMENT OF ACTIVE SUBSTANCES

Each film-coated tablet contains 61 mg micronized tafamidis.

3. LIST OF EXCIPIENTS

The film-coated tablet contains lactose monohydrate (E 24). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

3 x 10 film-coated tablets
9 x 10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

None.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
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Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/717/005	30 film-coated tablets
EU/1/11/717/006	90 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vyndaqel 61 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

Blisters for 61 mg Vyndaqel film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Vyndaqel 61 mg film-coated tablets
tafamidis

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Vyndaqel 20 mg soft capsules
tafamidis meglumine

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vyndaqel is and what it is used for
2. What you need to know before you take Vyndaqel
3. How to take Vyndaqel
4. Possible side effects
5. How to store Vyndaqel
6. Contents of the pack and other information

1. What Vyndaqel is and what it is used for

Vyndaqel contains the active substance tafamidis.

Vyndaqel is a medicine which treats a disease called transthyretin amyloidosis Transthyretin amyloidosis is caused by a protein called transthyretin (TTR) that does not work properly. TTR is a protein that carries other substances, such as hormones, through the body.

In patients with this disease, TTR breaks up and may form fibres called amyloid. Amyloid can build up around your nerves (known as transthyretin amyloid polyneuropathy or ATTR-PN) and in other places in your body. The amyloid causes the symptoms of this disease. When this occurs, it prevents them from working normally.

Vyndaqel, can prevent TTR from breaking up and forming amyloid. This medicine is used to treat adult patients with this disease whose nerves have been affected (people with symptomatic polyneuropathy) to delay further progression.

2. What you need to know before you take Vyndaqel

Do not take Vyndaqel

If you are allergic to tafamidis meglumine or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Vyndaqel.

- Women that can become pregnant should use birth control while taking Vyndaqel and should continue using birth control for one month after stopping treatment with Vyndaqel. There are no data on the use of Vyndaqel in pregnant women.

Children and adolescents

Children and adolescents do not have the symptoms of transthyretin amyloidosis. Vyndaqel is therefore not used for children and adolescents.

Other medicines and Vyndaqel

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should inform your doctor or pharmacist if you are taking any of the following:

- non-steroidal anti-inflammatory drugs
- diuretic medicines (e.g. furosemide, bumetanide)
- anti-cancer medicines (e.g. methotrexate, imatinib)
- statins (e.g. rosuvastatin, atorvastatin)
- anti-clotting medicines (e.g. apixaban, rivaroxaban)
- anti-viral medicines (e.g. oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, lamivudine, zidovudine, zalcitabine)

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- You should not take Vyndaqel if you are pregnant or breast-feeding.
- If you are able to become pregnant, you must use birth control during treatment and for one month after stopping treatment.

Driving and using machines

Vyndaqel is believed to have no or negligible influence on the ability to drive and use machines.

Vyndaqel contains sorbitol

This medicine contains no more than 44 mg sorbitol in each capsule. Sorbitol is a source of fructose.

3. How to take Vyndaqel

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one Vyndaqel 20 mg (tafamidis meglumine) capsule taken once a day.

If you vomit after taking this medicine and can identify the intact Vyndaqel capsule, then an additional dose of Vyndaqel should be taken in the same day; if you cannot identify the Vyndaqel capsule, then no additional dose of Vyndaqel is necessary, and you can resume taking Vyndaqel the next day as usual.

Method of administration

Vyndaqel is for oral use.
The soft capsule should be swallowed whole, not crushed or cut.
The capsule may be taken with or without food.

Instructions for opening the blisters

- Tear off one individual blister from the blister card along the perforated line.
- Push capsule through the aluminium foil.

If you take more Vyndaqel than you should

You should not take more capsules than your doctor tells you to. If you take more capsules than you have been told to take, contact your doctor.

If you forget to take Vyndaqel

If you forget to take a dose, take your capsules as soon as you remember. If it is within 6 hours before your next dose, skip the missed dose and take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Vyndaqel

Do not stop taking Vyndaqel without first speaking to your doctor. As Vyndaqel works by stabilising the TTR protein, if you stop taking Vyndaqel, the protein will no longer be stabilised, and your disease may progress.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common: may affect more than 1 in 10 people are listed below:
- Diarrhoea
- Urinary tract infection (symptoms may include: pain or a burning sensation when you urinate or a frequent need to urinate)
- Stomach ache or abdominal pain

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vyndaqel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister card and on the carton. The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vyndaqel contains

- The active substance is tafamidis. Each capsule contains 20 mg micronized tafamidis meglumine equivalent to 12.2 mg tafamidis.

- The other ingredients are: gelatine (E 441), glycerine (E 422), sorbitol (E 420) [see section 2 "Vyndaqel contains sorbitol"], mannitol (E 421), sorbitan, yellow iron oxide (E 172), titanium dioxide (E 171), purified water, macrogol 400 (E 1521), sorbitan monooleate (E 494), polysorbate 80 (E 433), ethyl alcohol, isopropyl alcohol, polyvinyl acetate phthalate, propylene glycol (E 1520), carmine (E 120), brilliant blue FCF (E 133) and ammonium hydroxide (E 527).

What Vyndaqel looks like and contents of the pack

Vyndaqel soft capsules are yellow, opaque, oblong (approximately 21 mm) printed with "VYN 20" in red. Vyndaqel is available in two pack sizes of PVC/PA/alu/PVC-alu perforated unit dose blisters: a pack of 30 x 1 soft capsules and a multipack of 90 soft capsules comprising of 3 cartons, each containing 30 x 1 soft capsules. Not all pack sizes may be marketed.

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Or

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Or

Pfizer Manufacturing Deutschland GmbH
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This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

This medicine has been authorised under 'exceptional circumstances'. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.

The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

If this leaflet is difficult to see or read or you would like it in a different format, please contact the Marketing Authorisation Holder's local office number that is provided in this leaflet.

Package leaflet: Information for the user

Vyndaqel 61 mg soft capsules
tafamidis

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vyndaqel is and what it is used for
2. What you need to know before you take Vyndaqel
3. How to take Vyndaqel
4. Possible side effects
5. How to store Vyndaqel
6. Contents of the pack and other information

1. What Vyndaqel is and what it is used for

Vyndaqel contains the active substance tafamidis.

Vyndaqel is a medicine which treats a disease called transthyretin amyloidosis. Transthyretin amyloidosis is caused by a protein called transthyretin (TTR) that does not work properly. TTR is a protein that carries other substances, such as hormones, through the body.

In patients with this disease, TTR breaks up and may form fibres called amyloid. Amyloid can build up between cells in your heart (known as transthyretin amyloid cardiomyopathy or ATTR-CM) and in other places in your body. The amyloid causes the symptoms of this disease. When this occurs in your heart, it prevents your heart from working normally.

Vyndaqel, can prevent TTR from breaking up and forming amyloid. This medicine is used to treat adult patients whose heart has been affected (people with symptomatic cardiomyopathy).

2. What you need to know before you take Vyndaqel

Do not take Vyndaqel

If you are allergic to tafamidis or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Vyndaqel.

- Women that can become pregnant should use birth control while taking Vyndaqel and should continue using birth control for one month after stopping treatment with Vyndaqel. There are no data on the use of Vyndaqel in pregnant women.

Children and adolescents

Children and adolescents do not have the symptoms of transthyretin amyloidosis. Vyndaqel is therefore not used for children and adolescents.

Other medicines and Vyndaqel

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should inform your doctor or pharmacist if you are taking any of the following:

- non-steroidal anti-inflammatory drugs
- diuretic medicines (e.g. furosemide, bumetanide)
- anti-cancer medicines (e.g. methotrexate, imatinib)
- statins (e.g. rosuvastatin, atorvastatin)
- anti-clotting medicines (e.g. apixaban, rivaroxaban)
- anti-viral medicines (e.g. oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, lamivudine, zidovudine, zalcitabine)

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- You should not take Vyndaqel if you are pregnant or breast-feeding.
- If you are able to become pregnant, you must use birth control during treatment and for one month after stopping treatment.

Driving and using machines

Vyndaqel is believed to have no or negligible influence on the ability to drive and use machines.

Vyndaqel contains sorbitol

This medicine contains no more than 44 mg sorbitol in each capsule. Sorbitol is a source of fructose.

3. How to take Vyndaqel

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one Vyndaqel 61 mg (tafamidis) capsule taken once a day.

If you vomit after taking this medicine and can identify the intact Vyndaqel capsule, then an additional dose of Vyndaqel should be taken in the same day; if you cannot identify the Vyndaqel capsule, then no additional dose of Vyndaqel is necessary, and you can resume taking Vyndaqel the next day as usual.

Method of administration

Vyndaqel is for oral use.
The soft capsule should be swallowed whole, not crushed or cut.
The capsule may be taken with or without food.

Instructions for opening the blisters

- Tear off one individual blister from the blister card along the perforated line.
- Push capsule through the aluminium foil.

If you take more Vyndaqel than you should

You should not take more capsules than your doctor tells you to. If you take more capsules than you have been told to take, contact your doctor.

If you forget to take Vyndaqel

If you forget to take a dose, take your capsules as soon as you remember. If it is within 6 hours before your next dose, skip the missed dose and take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Vyndaqel

Do not stop taking Vyndaqel without first speaking to your doctor. As Vyndaqel works by stabilising the TTR protein, if you stop taking Vyndaqel, the protein will no longer be stabilised, and your disease may progress.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
- Diarrhoea
- Rash, itching

In clinical studies, the side effects in patients taking Vyndaqel were generally similar to that of patients not taking Vyndaqel. Flatulence and increase in liver function tests were reported more often in ATTR-CM patients treated with Vyndaqel.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vyndaqel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister card and on the carton. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vyndaqel contains

- The active substance is tafamidis. Each capsule contains 61 mg micronized tafamidis.
- The other ingredients are: gelatine (E 441), glycerine (E 422), sorbitol (E 420) [see section 2 "Vyndaqel contains sorbitol"], mannitol (E 421), sorbitan, red iron oxide (E 172), purified water, macrogol 400 (E 1521), polysorbate 20 (E 432), povidone (K-value 90), butylated hydroxytoluene (E321), ethyl alcohol, isopropyl alcohol, polyvinyl acetate phthalate, propylene glycol (E 1520), titanium dioxide (E 171), and ammonium hydroxide (E 527).

What Vyndaqel looks like and contents of the pack

Vyndaqel soft capsules are reddish brown, opaque, oblong (approximately 21 mm) printed with "VYN 61" in white. Vyndaqel is available in two pack sizes of PVC/PA/alu/PVC-alu perforated unit dose blisters: a pack of 30 x 1 soft capsules and a multipack of 90 soft capsules comprising of 3 cartons, each containing 30 x 1 soft capsules. Not all pack sizes may be marketed.

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This leaflet was last revised in <{MM/YYYY}>.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

If this leaflet is difficult to see or read or you would like it in a different format, please contact the Marketing Authorisation Holder's local office number that is provided in this leaflet.

Package leaflet: Information for the user

Vyndaqel 61 mg film-coated tablets
tafamidis

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vyndaqel is and what it is used for
2. What you need to know before you take Vyndaqel
3. How to take Vyndaqel
4. Possible side effects
5. How to store Vyndaqel
6. Contents of the pack and other information

1. What Vyndaqel is and what it is used for

Vyndaqel contains the active substance tafamidis.

Vyndaqel is a medicine which treats a disease called transthyretin amyloidosis. Transthyretin amyloidosis is caused by a protein called transthyretin (TTR) that does not work properly. TTR is a protein that carries other substances, such as hormones, through the body.

In patients with this disease, TTR breaks up and may form fibres called amyloid. Amyloid can build up between cells in your heart (known as transthyretin amyloid cardiomyopathy or ATTR-CM) and in other places in your body. The amyloid causes the symptoms of this disease. When this occurs in your heart, it prevents your heart from working normally.

Vyndaqel, can prevent TTR from breaking up and forming amyloid. This medicine is used to treat adult patients whose heart has been affected (people with symptomatic cardiomyopathy).

2. What you need to know before you take Vyndaqel

Do not take Vyndaqel

If you are allergic to tafamidis or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Vyndaqel.

- Women that can become pregnant should use birth control while taking Vyndaqel and should continue using birth control for one month after stopping treatment with Vyndaqel. There are no data on the use of Vyndaqel in pregnant women.

Children and adolescents

Children and adolescents do not have the symptoms of transthyretin amyloidosis. Vyndaqel is therefore not used for children and adolescents.

Other medicines and Vyndaqel

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should inform your doctor or pharmacist if you are taking any of the following:

- non-steroidal anti-inflammatory drugs
- diuretic medicines (e.g. furosemide, bumetanide)
- anti-cancer medicines (e.g. methotrexate, imatinib)
- statins (e.g. rosuvastatin, atorvastatin)
- anti-clotting medicines (e.g. apixaban, rivaroxaban)
- anti-viral medicines (e.g. oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, lamivudine, zidovudine, zalcitabine)

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- You should not take Vyndaqel if you are pregnant or breast-feeding.
- If you are able to become pregnant, you must use birth control during treatment and for one month after stopping treatment.

Driving and using machines

Vyndaqel is believed to have no or negligible influence on the ability to drive and use machines.

Vyndaqel contains lactose monohydrate

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Vyndaqel

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one Vyndaqel 61 mg (tafamidis) tablet taken once a day.

If you vomit after taking this medicine and can identify the intact Vyndaqel tablet, then an additional dose of Vyndaqel should be taken in the same day; if you cannot identify the Vyndaqel tablet, then no additional dose of Vyndaqel is necessary, and you can resume taking Vyndaqel the next day as usual.

<u>Method of administration</u>

Vyndaqel is for oral use.

The tablet should be swallowed whole, not crushed or cut.
The tablet may be taken with or without food.

Instructions for opening the blisters

Push tablet through the aluminium foil.

If you take more Vyndaqel than you should

You should not take more tablets than your doctor tells you to. If you take more tablets than you have been told to take, contact your doctor.

If you forget to take Vyndaqel

If you forget to take a dose, take your tablets as soon as you remember. If it is within 6 hours before your next dose, skip the missed dose and take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Vyndaqel

Do not stop taking Vyndaqel without first speaking to your doctor. As Vyndaqel works by stabilising the TTR protein, if you stop taking Vyndaqel, the protein will no longer be stabilised, and your disease may progress.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
- Diarrhoea
- Rash, itching

In clinical studies, the side effects in patients taking Vyndaqel were generally similar to that of patients not taking Vyndaqel. Flatulence and increase in liver function tests were reported more often in ATTR-CM patients treated with Vyndaqel.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vyndaqel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister card and on the carton. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vyndaqel contains

- The active substance is tafamidis. Each tablet contains 61 mg micronized tafamidis.
- The other ingredients are: microcrystalline cellulose (E 460), lactose monohydrate (E 24) [see section 2 "Vyndaqel contains lactose monohydrate"], crospovidone (E 1202), magnesium stearate (E 470b), calcium carbonate, isomalt, hypromellose, and medium-chain triglycerides.

What Vyndaqel looks like and contents of the pack

Vyndaqel film-coated tablets are 11 mm round white to off-white and embossed with "61" on one side. Vyndaqel is available in two pack sizes of OPA/Al/PVC-alu blisters.

Pack sizes: a pack of 3 x 10 film-coated tablets and a pack of 9 x 10 film-coated tablets.

Not all pack sizes may be marketed.

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