Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document

Information for the healthcare professionals:

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 transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation.

4.2 Posology and method of administration

Treatment should be initiated by and remain under the supervision of a physician knowledgeable in the management of patients with transthyretin amyloid cardiomyopathy (ATTR-CM).

Posology

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

A single 61 mg tafamidis capsule is bioequivalent to 80 mg tafamidis meglumine (four 20 mg tafamidis meglumine capsules) and is not interchangeable on a per mg basis (see sections 5.1 and 5.2).

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 amyloid cardiomyopathy. 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.

This medicinal product contains 44 mg sorbitol in each capsule.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

In vitro data also indicated that tafamidis does not significantly inhibit cytochrome P450 enzymes CYP1A2, CYP3A4, CYP3A5, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. In addition, tafamidis did not induce CYP1A2, but did induce CYP2B6 *in vitro*, however based on the negative clinical CYP3A4 induction results, it can be concluded that the likelihood of CYP2B6 clinical induction is low.

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.

In vitro tafamidis inhibits the efflux transporter BCRP (breast cancer resistant protein) 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, imatinib) following a 61 mg/day tafamidis dose. 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). However, additional risk assessments based on the R-value model ($AUCi/AUC=1+(C_{max},u/Ki)$) were performed and 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.

4.6 Fertility, pregnancy and lactation

<u>Women of childbearing potential</u>

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.

To monitor outcomes of pregnant women exposed to Vyndaqel, a Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) programme has been established. Physicians are encouraged to report pregnancies occurring in women who are being treated with Vyndaqel. TESPO is a voluntary program to collect safety data (including major birth defects or other developmental abnormalities in live born children) in female patients with transthyretin amyloidosis who are exposed to Vyndaqel during or within 1 month prior to their pregnancy. Healthcare professionals caring for patients who become pregnant during or within 1 month of exposure to Vyndaqel are asked to report the pregnancy to Pfizer by contacting the Pfizer Drug Safety Unit by email: GBR.AEReporting@pfizer.com.

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

Transthyretin amyloid cardiomyopathy

Summary of the safety profile

The data across clinical trials reflect exposure of 377 ATTR-CM patients to 20 mg or 80 mg (administered as 4 x 20 mg) of tafamidis meglumine administered daily for an average of 24.5 months (ranging from 1 day to 111 months). The population included adult patients diagnosed with ATTR-CM, the majority (approximately 90%) of which had a baseline NYHA (New York Heart Association) classification of Class II or Class III. The mean age was approximately 75 years (ranging from 46 years to 91 years of age); a majority were male (> 90%), and approximately 82% were Caucasian.

Adverse events were assessed from ATTR-CM clinical trials with tafamidis meglumine including 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 20 mg or 80 mg (administered as 4 x 20 mg) of tafamidis meglumine was similar and comparable to placebo. No adverse events were identified as adverse drug reactions associated with Vyndaqel administration in this population.

A lower proportion of tafamidis meglumine-treated patients compared to placebo discontinued due to an adverse event in the 30-month placebo-controlled trial in patients diagnosed with ATTR-CM [40 (22.7%),

16 (18.2%), and 51 (28.8%) patients from the 80 mg tafamidis meglumine (administered as 4 x 20 mg), 20 mg tafamidis meglumine, and placebo groups, respectively].

Tabulated list of adverse events occurring in ≥10% of either the pooled tafamidis or placebo groups.

Adverse events are listed below by MedDRA System Organ Class (SOC). Adverse events 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 (B3461028).

System Organ Class	Placebo (N=177), n (%)	Tafamidis 20 mg + 80 mg (N=264), n (%)
CARDIAC DISORDERS		
Atrial fibrillation	33 (18.6)	50 (18.9)
Cardiac failure	60 (33.9)	76 (28.8)
Cardiac failure acute	17 (9.6)	28 (10.6)
Cardiac failure congestive	33 (18.6)	39 (14.8)
GASTROINTESTINAL DISORDERS		
Constipation	30 (16.9)	40 (15.2)
Diarrhoea	39 (22.0)	32 (12.1)
Nausea	36 (20.3)	29 (11.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Asthenia	11 (6.2)	29 (11.0)
Fatigue	33 (18.6)	45 (17.0)
Oedema	19 (10.7)	18 (6.8)
Oedema peripheral	31 (17.5)	47 (17.8)
INFECTIONS AND INFESTATIONS		
Bronchitis	19 (10.7)	30 (11.4)
Pneumonia	17 (9.6)	33 (12.5)
Urinary tract infection	27 (15.3)	25 (9.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Fall	41 (23.2)	70 (26.5)
INVESTIGATIONS		
Weight decreased	18 (10.2)	14 (5.3)
METABOLISM AND NUTRITIONAL DISORDERS		
Decreased appetite	25 (14.1)	22 (8.3)
Fluid overload	29 (16.4)	32 (12.1)
Gout	29 (16.4)	28 (10.6)
Hypokalaemia	19 (10.7)	24 (9.1)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia	21 (11.9)	26 (9.8)
Back pain	24 (13.6)	26 (9.8)
Pain in extremity	20 (11.3)	33 (12.5)
NERVOUS SYSTEM DISORDERS		
Dizziness	37 (20.9)	42 (15.9)
PSYCHIATRIC DISORDERS		
Insomnia	22 (12.4)	32 (12.1)
RENAL AND URINARY DISORDERS		
Acute kidney injury	29 (16.4)	29 (11.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough	29 (16.4)	37 (14.0)
Dyspnoea	54 (30.5)	50 (18.9)
Pleural effusion	32 (18.1)	26 (9.8)
VASCULAR DISORDERS		
Hypotension	19 (10.7)	31 (11.7)

Transthyretin amyloid polyneuropathy

Summary of the safety profile

The overall clinical data reflect exposure of 127 TTR amyloid polyneuropathy patients 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
	Vaginal 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 Compassionate Use Adverse Event form to Pfizer within 24 hours of awareness of the event for assessment and processing. The contact details for the Pfizer Drug Safety Unit are:
GBR.AEReporting@pfizer.com.

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. PHARMACOLOGICAL 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 reduce all-cause mortality and cardiovascular-related hospitalisation 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.

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. Tafamidis 61 mg is bioequivalent to tafamidis meglumine 80 mg (see section 5.2). 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).

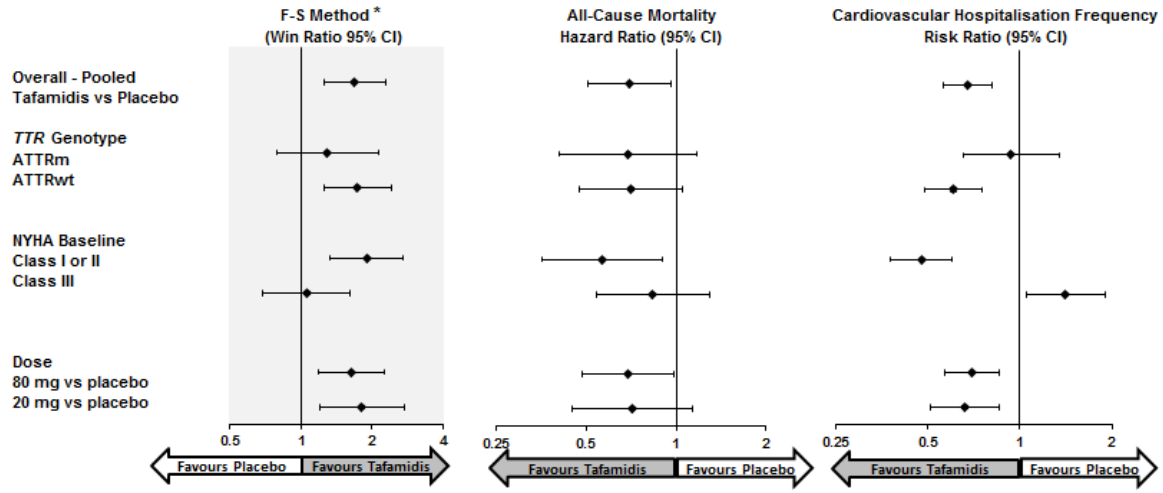
There were significantly fewer cardiovascular-related hospitalisations with tafamidis compared with placebo with a reduction in risk of 32.4% (p<0.0001).

The treatment effect of tafamidis on functional capacity and health status was assessed by the 6-Minute Walk Test (6MWT) and the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score, respectively. A significant treatment effect favouring tafamidis was first observed at Month 6 and remained consistent through Month 30 on both 6MWT distance and KCCQ-OS score (p<0.0001 at Month 30 for both endpoints.

At Month 1, a significantly greater proportion of patients in the pooled tafamidis group (211/245 [86.1%] patients) demonstrated TTR stabilisation than was observed for patients in the placebo group (6/170 [3.5%] patients) (p< 0.0001).

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 across all subgroups (wild-type, variant and NYHA Class I & II, and III) except for cardiovascular-related hospitalisation frequency in NYHA Class III (Figure 4). Win ratio is the number of pairs of treated-patient "wins" divided by number of pairs of placebo patient "wins." Analyses of 6MWT and KCCQ-OS also favoured tafamidis relative to placebo within each subgroup.

Figure 4: 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).
Heart transplants and cardiac mechanical assist devices treated as death.

Biomarkers associated with heart failure (NT-proBNP and Troponin I) differentiated between the 80 mg and the 20 mg doses. For NT-proBNP, the LS mean difference in change from Baseline to Month 30 from placebo for tafamidis meglumine 20 mg was -1417.02 pg/mL (SE=743.38) and for 80 mg was -2587.54 pg/mL (SE=570.25). Further, the LS mean difference between the 20 mg and 80 mg doses was 1170.51 pg/mL (SE=587.31) (p=0.0468), favouring the 80 mg dose group. Similar results were observed for Troponin I where the LS mean difference in change from Baseline to Month 30 from placebo for tafamidis meglumine 20 mg was -0.06 ng/mL (SE=0.045) and for 80 mg was -0.10 ng/mL (SE=0.018). The LS mean difference between the 20 mg and 80 mg doses for Troponin I was 0.05 ng/mL (SE=0.04) (p=0.2479), favouring the 80 mg dose group.

In a comparison of all-cause mortality in the extension study by dose, the Hazard Ratio was 0.8976 (95% CI 0.5711, 1.4108), indicating a 10.2% reduction in risk of death in patients receiving 80 mg relative to patients receiving 20 mg (p=0.6395).

5.2 Pharmacokinetic properties

Absorption

After oral administration of the soft capsule once daily, the maximum peak concentration (C_{max}) is achieved at 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 approximately 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 1,000-fold greater than that for albumin. Therefore, tafamidis binds preferentially to TTR despite the significantly higher concentration of albumin (600 μM) relative to TTR (3.6 μM) in plasma.

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.

Tafamidis 61 mg provides steady-state exposures (C_{max} and AUC) equivalent to tafamidis meglumine 80 mg (administered as four 20 mg capsules), which was administered to patients with ATTR-CM in the double-blind, placebo-controlled, randomised study (Table 5) (see section 5.1).

Table 5: Comparative pharmacokinetics of tafamidis 61 mg capsule to tafamidis meglumine 80 mg (administered as four 20 mg capsules)

Parameter (units)	Comparison (test versus reference)	Adjusted geometric means		Test versus reference	
		Test	Reference	Ratio (%)[a] (test/reference)	90% CI[a] for ratio
AUC_{tau} (μg.hr/mL)	Tafamidis 61 mg capsule (Test) versus Tafamidis meglumine Four 20 mg capsules (Reference)	170.0	166.2	102.28	(97.99, 106.76)
C_{max} (μg/mL)		8.553	9.087	94.12	(89.09, 99.42)

Abbreviations: CI=confidence interval; mg=milligram; μg=microgram; mL=millilitre; AUC_{tau}=area under curve from time 0 to time tau, the dosing interval, where tau=24 hours for daily dosing; C_{max}=maximum serum concentration.
[a] The ratios and 90% CIs are expressed as percentages.

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.

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 ≥ 0.7 times 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 0.9 times 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

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

HDPE bottle containing 40 soft capsules.

6.6 Special precautions for disposal and other handling

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

7. SCIENTIFIC OPINION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent
CT13 9NJ
United Kingdom

8. EAMS NUMBER

00057/0004

9. DATE OF SCIENTIFIC OPINION

May 2019

Additional information:

Each prescribing clinician and pharmacist involved in the patients treatment must Register and agree to the terms of Adverse events reporting. They will have to complete a short **Initial Drug Supply and electronic Case Report Form.**

An **Informed Consent Form** (ICF) will be provided by Pfizer to be completed with the patient.

A **Letter of Agreement** (LOA) will be signed by the prescribing physician and a legal representative from the trust.

Pfizer will arrange training (including adverse event training) and delivery of the programme materials.

A **Drug Re-supply and electronic Case Report Form** will be accessible online to order further drug supplies. The prescribing physician will be required to complete **the Drug Re-supply and Case Report Form** every three months to order the prescription of tafamidis for their patient. The order should be placed at least two weeks before the next planned prescription is due.

The prescribing physician is requested to inform Pfizer if a patient discontinues treatment by completing the electronic Case Report Form with the date of the patient's last treatment and dose.

Contact information:

To initiate the registration process for EAMS you are required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the date of birth of the patient, complete the inclusion / exclusion criteria and the **Informed Consent Form (ICF)** through the Tafamidis EAMS website (PfizerEAMS.co.uk). The step by step details on access to tafamidis, training on adverse events reporting and all forms will be accessible through this site.

For NHS England:

If the patient is eligible and in England, and once eligibility is confirmed by Pfizer Medical Employees, the HCP will also register the patient with NHS England through the online Blueteq system. The site personnel will then be provided with an EAMS number by NHS England. This EAMS number will then be provided to Pfizer alongside the **Initial Drug Supply Form** to initiate a treatment assignment and dispensable unit (DU) or container number.

For NHS Wales, Scotland and Northern Ireland:

The prescribing physician can complete the **Initial Drug Supply Form** during the registration process and will be provided with an EAMS number by Pfizer. There is no requirement to register patients through the online Bluetec system in Wales, Scotland and Northern Ireland.

Additional contact:
Pfizer Medical Information on +44 (0) 1304 616161 or Medical.Information@pfizer.com