▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/safety/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – VYNDAMAX® (tafamidis) soft capsules

1. NAME OF THE MEDICINE

Tafamidis

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The drug product is a soft capsule containing 61 mg micronised tafamidis.

Each soft capsule contains no more than 44 mg of sorbitol.

The soft capsules contain sulfites.

For the full list of excipients, see Section 6.1 List of excipients.

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

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

4.2 Dose and method of administration

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

Dosage

The recommended dose of VYNDAMAX is 61 mg tafamidis orally once daily (see Section 5.1 Pharmacodynamic properties).

A single 61 mg VYNDAMAX (tafamidis) capsule is bioequivalent to 80 mg VYNDAQEL (tafamidis meglumine) (administered as four 20 mg VYNDAQEL capsules) and is not

interchangeable on a per mg basis (see Section 5.1 Pharmacodynamic properties and Section 5.2 Pharmacokinetic properties).

No dose ranging studies have been undertaken.

Method of administration

Oral use.

The capsule(s) should be swallowed whole and not crushed or cut. VYNDAMAX may be taken with or without food.

If a dose is missed, the patient should take the dose as soon as remembered. If it is almost time for the next dose, the patient should skip the missed dose and take the next dose at the regularly scheduled time. Do not double the dose.

Dosage adjustment

Renal or hepatic impairment

No dosage adjustment is required for patients with renal impairment, or mild or moderate hepatic impairment. VYNDAMAX has not been studied in patients with severe hepatic impairment (see Section 5.2 Pharmacokinetic properties).

Elderly

No dosage adjustment is required for elderly patients (≥65 years) (see Section 5.2 Pharmacokinetic properties). Of the total number of patients in the clinical study (n=441), 90.5% were 65 and over, with a median age of 75 years.

Paediatric

The safety and effectiveness of VYNDAMAX have not been established in paediatric patients.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of VYNDAMAX listed in Section 6.1 List of excipients.

4.4 Special warnings and precautions for use

Women of childbearing potential

Studies in animals have shown developmental toxicity (see Section 4.6 Fertility, pregnancy and lactation). The potential risk for humans is unknown. VYNDAMAX is not recommended during pregnancy. Women of childbearing potential should use appropriate contraception when taking VYNDAMAX and continue to use appropriate contraception for 1-month after stopping treatment with VYNDAMAX (see Section 4.6 Fertility, pregnancy and lactation).

Organ transplant patients

A study has not been conducted in organ transplant patients. The efficacy and safety of VYNDAMAX in organ transplant patients has not been established.

BCRP substrates

Based on the potential of VYNDAMAX to inhibit the efflux transporter BCRP (breast cancer resistant protein), caution should be used when co-administering VYNDAMAX and BCRP substrates, because of the risk of BCRP substrate related adverse reactions (see Section 4.5 Interactions with other medicines and other forms of interactions).

Sorbitol

This medicinal product contains no more than 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.

Liver function tests

Increase in liver function tests may occur (see Section 4.8 Adverse effects (undesirable effects)).

Use in hepatic impairment

Tafamidis has not been studied in patients with severe hepatic impairment and caution is recommended (see Section 5.2 Pharmacokinetic properties).

Use in renal impairment

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

Use in the elderly

See Section 4.2 Dose and method of administration.

Paediatric use

See Section 4.2 Dose and method of administration.

Effects on laboratory tests

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 (see Section 4.8 Adverse effects (undesirable effects)).

The incidence of thyroxine abnormality <0.8 x Lower Level of Normal (LLN) was greater in the tafamidis meglumine 80 mg group (29.7%) than in the tafamidis meglumine 20 mg (12.3%) and placebo (4.5%) groups.

4.5 Interactions with other medicines and other forms of interactions

In a clinical study in healthy volunteers, tafamidis meglumine 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.

Tafamidis has the potential to inhibit the efflux transporter BCRP and may increase systemic exposure of 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 doses of 61 mg tafamidis daily dosing. Dose adjustment may be needed for these substrates.

Patients should be carefully monitored for BCRP substrate related adverse reactions when used concomitantly with VYNDAMAX. A dose modification of the BCRP substrate according to its Prescribing Information should be considered.

Tafamidis may have the potential to inhibit organic anion transporter 1 (OAT1) and OAT3 and may cause drug-drug interactions 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 61 mg tafamidis daily dose, therefore, inhibition of OAT1 or OAT3 transporters by tafamidis is not expected to result in clinically significant interactions.

Patients receiving substrates of both BCRP and OAT with tafamidis should be assessed as exposure of these drugs may be increased e.g., methotrexate AUC might be increased by ~50%.

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

No significant effect was observed on the pharmacokinetics of midazolam (a CYP3A4 substrate) or on the formation of its active metabolite (1-hydroxymidazolam), when a single 7.5 mg dose of midazolam was administered prior to and after a 14-day regimen of 20 mg once-daily tafamidis meglumine. The overall systemic exposure ($AUC_{0-\infty}$) and total clearance

(CL/F) of midazolam were shown to be equivalent. In addition, tafamidis did not induce CYP3A4 activity in either male or female subjects.

4.6 Fertility, pregnancy and lactation

Effects on fertility

There were no effects of tafamidis meglumine on fertility, reproductive performance, or mating behavior in the rat at any dose. Rats were dosed daily (5, 15, and 30 mg/kg/day) prior to cohabitation (for at least 15 days for females and 28 days for males), throughout the cohabitation period to the day prior to termination of males and through to implantation of females (Gestation Day 7). No adverse effects were noted on male rats in toxicity, fertility and mating behaviour at any dose. Because no reproductive effects occurred at the highest dose tested, the paternal and maternal no observed effect level for reproductive toxicity of tafamidis meglumine is greater than 30 mg/kg/day (9.5-times the clinical AUC at the MRHD of 61 mg tafamidis per day).

Developmental toxicity

In pregnant rabbits increased skeletal variations were observed at ≥0.5 mg/kg/day (exposures approximately equivalent to clinical exposures at the MRHD of 61 mg tafamidis), while increased skeletal malformations, reduced embryo-fetal survival and reduction in fetal body weights were observed at 8 mg/kg/day (AUC exposures ≥9.1-times clinical AUC at the MRHD). In pregnant rats, oral administration of tafamidis (15, 30, and 45 mg/kg/day) from Gestation Day 7 through 17 resulted in decreased fetal weights at ≥30 mg/kg/day (approximately ≥9.5-times the human AUC at the clinical dose of 61 mg tafamidis).

In the rat pre- and post-natal development study with tafamidis, pregnant rats were orally administered tafamidis meglumine at doses of 5, 15, or 30 mg/kg/day from Gestation Day 7 through Lactation Day 20. Decreased pup survival, reduced pup weights and malformations (microphthalmia, enophthalmos, domed head) were noted at doses ≥15 mg/kg/day (≥6.4-times the clinical AUC at the MRHD of 61 mg tafamidis per 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 no observable adverse effect level (NOAEL) for viability and growth in the F1 generation offspring following maternal exposures to tafamidis was 5 mg/kg/day (human equivalent dose of 0.8 mg/kg/day), a dose approximately 0.92-times the clinical dose of 61 mg tafamidis for a 70 kg adult.

Use in pregnancy – Pregnancy Category D

Women of childbearing potential

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

VYNDAMAX is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are no adequate data on the use of VYNDAMAX in pregnant women. Based on findings from animal studies, VYNDAMAX may cause fetal harm when administered to pregnant

women (see above). The potential risk for humans is unknown. VYNDAMAX is not recommended during pregnancy.

To monitor outcomes of pregnant women exposed to VYNDAMAX, a Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) program has been established. If a pregnancy occurs in a woman being treated with VYNDAMAX, medical or healthcare professionals are encouraged to report the pregnancy to the Sponsor (see Section 8 Sponsor).

Use in lactation

Nonclinical data demonstrate that tafamidis is secreted in the milk of lactating rats. While the effect of VYNDAMAX on nursing infants after administration to the mother has not been studied, a risk to infants cannot be excluded. Breastfeeding is not recommended during treatment with VYNDAMAX.

4.7 Effects on ability to drive and use machines

No studies on the effects of VYNDAMAX on the ability to drive or use machines have been performed.

4.8 Adverse effects (undesirable effects)

The data across clinical trials reflect exposure of 377 ATTR-CM patients to either 20 mg or 80 mg (administered as four 20 mg capsules) of tafamidis meglumine daily for an average of 24.5 months (ranging from 1 day to 111 months). Tafamidis 61 mg (VYNDAMAX) was not administered in the pivotal study (see Section 5.2 Pharmacokinetic properties). The population included adult patients diagnosed with ATTR-CM, the majority (approximately 90%) of whom 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 Pharmacodynamic properties). The frequency of adverse events in patients treated with 20 mg or 80 mg tafamidis meglumine was similar and comparable to placebo.

The most commonly reported treatment-emergent adverse events (>15%) for the patients treated with tafamidis meglumine (pooled tafamidis meglumine 20 mg + 80 mg) compared to placebo in the pivotal phase 3 Study B3461028 are shown in Table 1.

Table 1: Most common treatment-emergent adverse events (>15%) for patients treated with tafamidis meglumine in study B3461028

	Pooled tafamidis meglumine (20 mg + 80 mg) (N=264)	**Placebo (N=177)**
Cardiac failure	28.8%	33.9%
Fall	26.5%	23.2%
Atrial fibrillation	18.9%	18.6%
Dyspnoea	18.9%	30.5%
Peripheral oedema	17.8%	17.5%
Fatigue	17.0%	18.6%

Dizziness	15.9%	20.9%
Constipation	15.2%	16.9%

The treatment-emergent adverse events with a greater incidence in patients treated with tafamidis meglumine (pooled tafamidis meglumine 20 mg + 80 mg) than placebo in the pivotal phase 3 Study B3461028 are shown in Table 2.

Table 2: Treatment-emergent adverse events with a greater incidence in patients treated with tafamidis meglumine than placebo in study B3461028*

	Pooled tafamidis meglumine (20 mg + 80 mg) (N=264) n (%)	**Placebo (N=177) n (%)**
Asthenia	29 (11.0)	11 (6.2)
Balance disorder	17 (6.4)	2 (1.1)
Sinusitis	15 (5.7)	1 (0.6)
Cataract	12 (4.5)	2 (1.1%)
Flatulence	10 (3.8)	3 (1.7%)
Myalgia	10 (3.8)	2 (1.1)
Skin ulcer	10 (3.8)	1 (0.6)
Arthritis	8 (3.0)	1 (0.6)
Cystitis	8 (3.0)	0
Hyperhidrosis	6 (2.3)	0

* Adverse events are presented, regardless of causality, with an incidence at least twice placebo and at least four patients reporting the event.

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%) from the tafamidis meglumine 80 mg (administered as four 20 mg capsules), tafamidis meglumine 20 mg, and placebo groups, respectively].

Incidence of hypothyroidism was reported in 6.8%, 5.7% and 5.6% patients in the tafamidis meglumine 80 mg, 20 mg and placebo groups, respectively (see Section 4.4 Special warnings and precautions for use).

Liver function test increased were more frequent in the tafamidis meglumine 80 mg group (3.4%) than in the tafamidis meglumine 20 mg (2.3%) and placebo (1.1%) groups. A causal relationship has not been established (see Section 4.4 Special warnings and precautions for use).

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

Post-marketing experience

The Adverse Drug Reactions (ADRs) listed below are identified post-marketing, and are presented by MedDRA System Organ Class (SOC) and frequency categories, defined using the following convention: very common (≥10%), common (≥1% to <10%), uncommon (≥0.1% to <1%), rare (≥0.01% to <0.1%) or very rare (<0.01%).

Gastrointestinal disorders:

Common: Diarrhoea.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/safety/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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 with negative cooperativity to the two thyroxine binding sites on the native tetrameric form of TTR preventing dissociation into monomers, the rate-limiting step in the amyloidogenic process. The inhibition of TTR tetramer dissociation forms the rationale for the use of VYNDAMAX to reduce all-cause mortality and cardiovascular-related hospitalisation in ATTR-CM patients.

No studies have been undertaken to establish a direct relationship between this dissociation and an effect on reduction of amyloid deposition in the heart.

Pharmacodynamic effects

A TTR stabilisation assay was utilised as a pharmacodynamic marker and assessed the stability of the TTR tetramer under denaturation conditions. The TTR stabilisation assay quantifies immunoturbidimetric measurement of the stable TTR tetramer in plasma pre- and post-treatment with 2-day *in vitro* denaturation with urea. Using this assay, a dose-dependent trend for greater TTR tetramer stabilisation is observed for tafamidis meglumine 80 mg

compared to tafamidis meglumine 20 mg. However, the clinical relevance of a higher TTR tetramer stabilisation towards cardiovascular outcomes is not known.

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

A population PK/PD analysis was conducted with a database consisting of 3,662 observations from 102 healthy subjects and 558 patients with transthyretin amyloidosis.

None of the following parameters were found to modify the tafamidis meglumine pharmacodynamic response: race (non-Japanese vs. Japanese), patient type, or genotype.

Clinical trials

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.

Eligible patients were between 18 and 90 years old at the time of randomisation with a medical history of heart failure and documented ATTR-CM (variant or wild-type). Patients had documented presence of amyloid deposits in biopsy tissue and demonstration of TTR precursor protein at screening or previously, end-diastolic intraventricular septal wall thickness >12 mm by echocardiography, N-terminal prohormone B-type natriuretic peptide (NT-proBNP) ≥600 pg/mL and 6-Minute Walk Test (6MWT) >100 m at screening. Patients with NYHA Class I-III were enrolled, whilst patients with NYHA Class IV or transplant patients were excluded.

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).

Tafamidis 61 mg (VYNDAMAX) was not administered in the pivotal study (see Section 5.2 Pharmacokinetic properties).

Table 3 describes the patient demographics and baseline characteristics.

Table 3: Patient demographics and baseline characteristics

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

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

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

The primary analysis used the Finkelstein-Schoenfeld (F-S) method to perform a hierarchical combination of 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 F-S method compared each patient to every other patient within each stratum in a pair-wise manner to determine which member of the pair had experienced a more favourable outcome (i.e., "won"), proceeding in a hierarchical fashion using all-cause mortality followed by frequency of cardiovascular-related hospitalisations when patients could not 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 meglumine 20 mg and 80 mg dose group versus placebo (Table 4).

Table 4: Primary analysis using Finkelstein-Schoenfeld (F-S) Method of all-cause mortality and frequency of cardiovascular-related hospitalisations

Primary analysis	Pooled tafamidis meglumine 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	

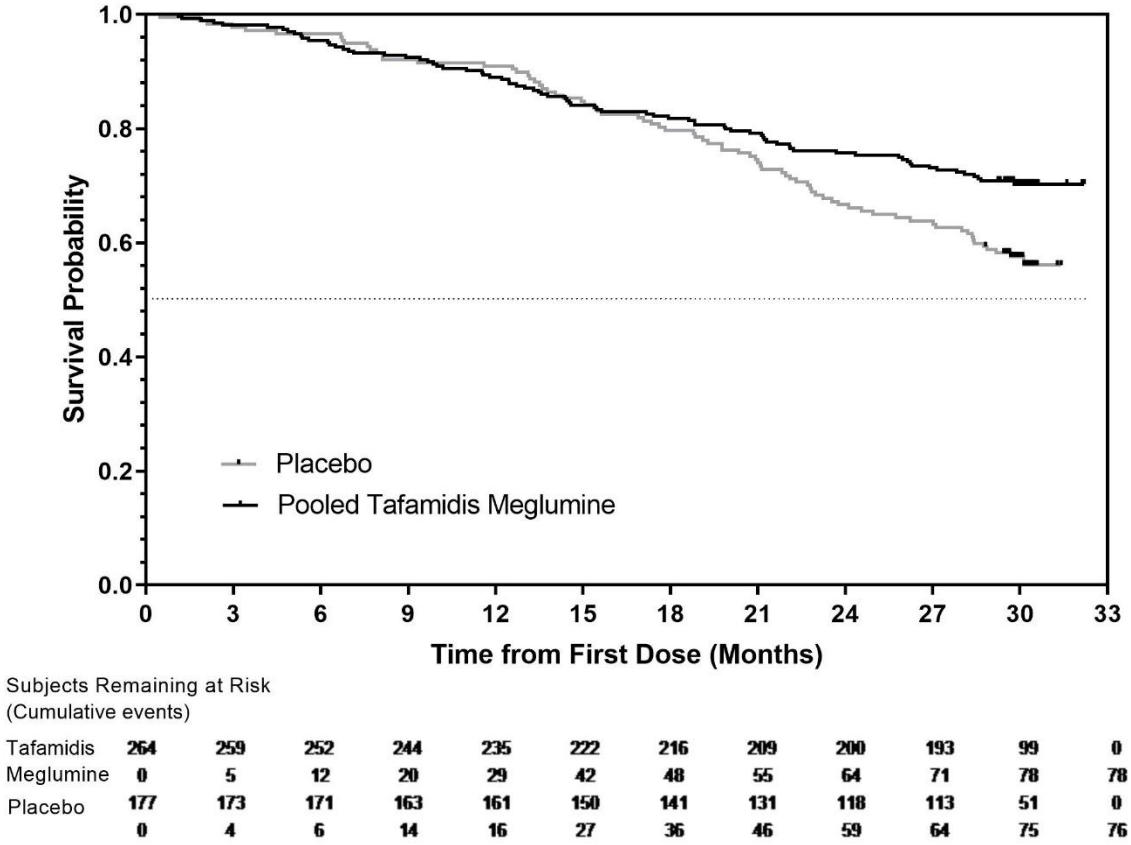
* Heart transplantation and cardiac mechanical assist device implantation are considered indicators of approaching end stage. As such, these subjects are treated in the analysis as equivalent to death. Therefore, such subjects are not included in the count of "Number of Subjects Alive at Month 30" even 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 meglumine versus placebo.

The hazard ratio from the all-cause mortality Cox-proportional hazard model for pooled tafamidis meglumine 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). Approximately 80% of total deaths were cardiovascular-related in both treatment groups. A Kaplan-Meier plot of time to event all-cause mortality is presented in Figure 1.

Figure 1: All-cause mortality*



* 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 meglumine compared with placebo with a reduction in risk of 32.4% (Table 5).

Table 5: Cardiovascular-related hospitalisation frequency

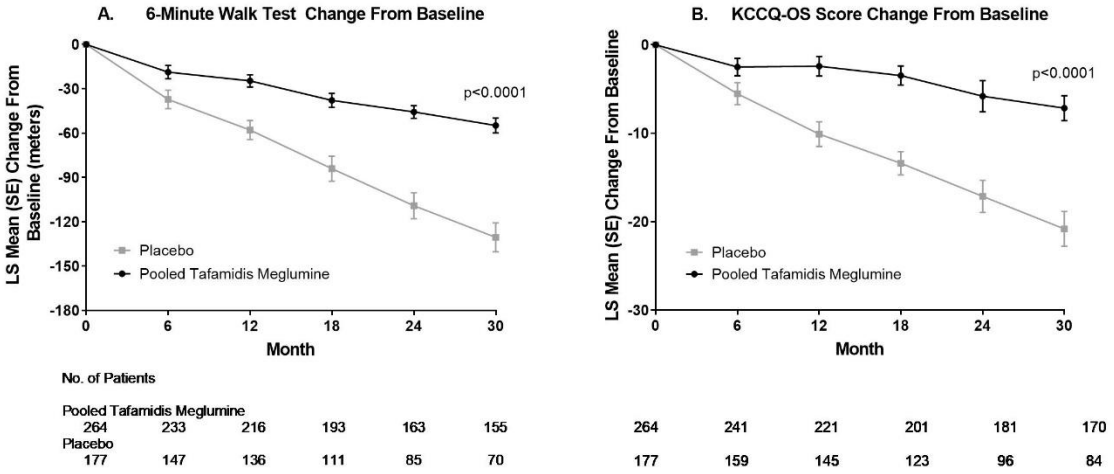
	Pooled tafamidis meglumine N=264	**Placebo N=177**
Total (%) number of subjects with cardiovascular-related hospitalisations	138 (52.3)	107 (60.5)
Cardiovascular-related hospitalisations per year*	0.4750	0.7025
Pooled tafamidis meglumine versus placebo treatment difference (relative risk ratio)*	0.6761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

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

The treatment effect of tafamidis meglumine 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 meglumine was first observed at Month 6 and remained consistent through Month 30 on both 6MWT distance and KCCQ-OS score (Figure 2 and Table 6).

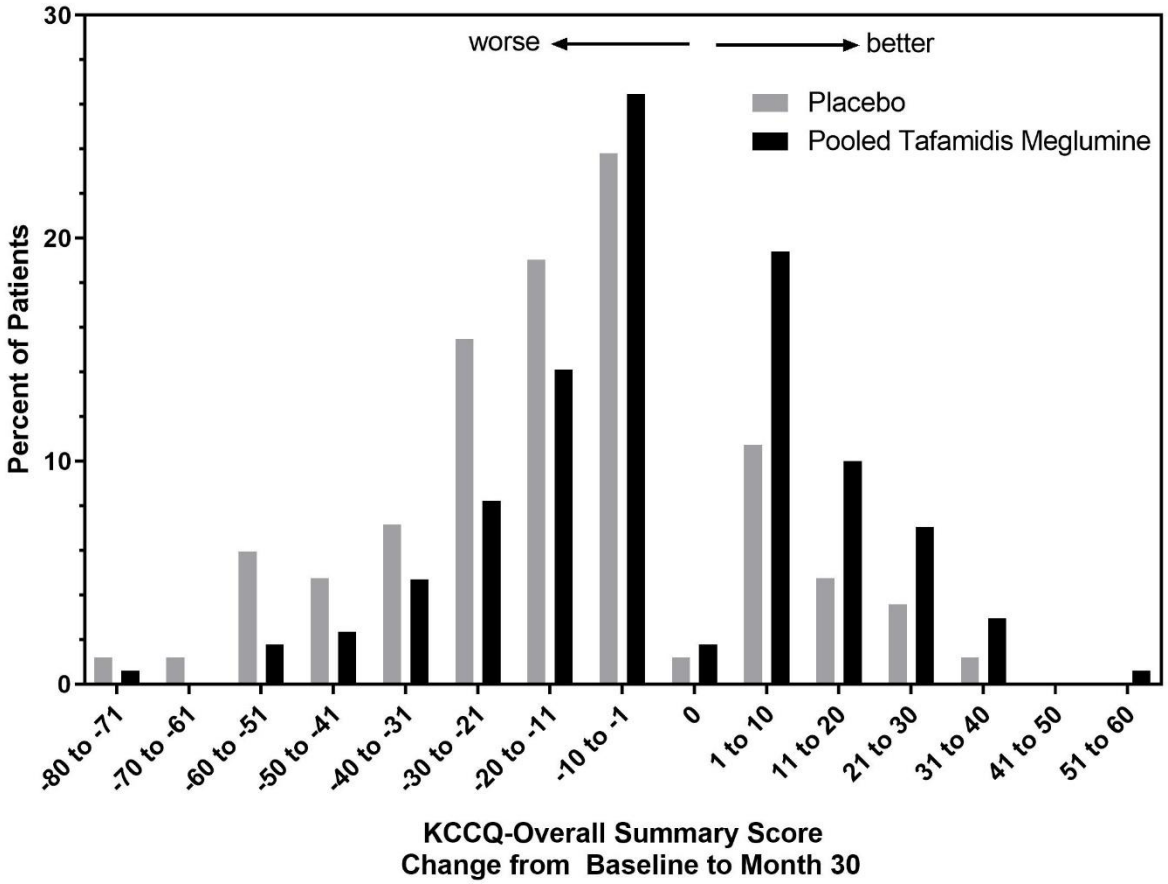
Figure 2: Change from Baseline to Month 30 in 6MWT distance and KCCQ-OS score



Abbreviations: 6MWT=6-Minute Walk Test, KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary.
Panel A shows change from Baseline to Month 30 in pooled tafamidis meglumine compared with placebo-treated patients in 6MWT distance.
Panel B shows change from Baseline to Month 30 in pooled tafamidis meglumine compared with placebo-treated patients in KCCQ-OS score.

The KCCQ-OS score is composed of four domains including Total Symptom (Symptom Frequency and Symptom Burden), Physical Limitation, Quality of Life, and Social Limitation. All four domains favoured tafamidis meglumine compared to placebo at Month 30 (Figure 2 and Table 6). KCCQ-OS and domain scores range from 0-100 with higher scores representing better health status. The cumulative distribution and distribution for change from Baseline to Month 30 for KCCQ-OS (Figure 3) show that the proportion of patients with declining KCCQ-OS scores was lower for the pooled tafamidis meglumine treated group compared to placebo (Figure 3).

Figure 3: Histogram of change from Baseline to Month 30 in KCCQ-OS



Abbreviation: KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary.

Table 6: 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 meglumine N=264	**Placebo N=177**	**Pooled tafamidis meglumine**	**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)	$p<0.0001$

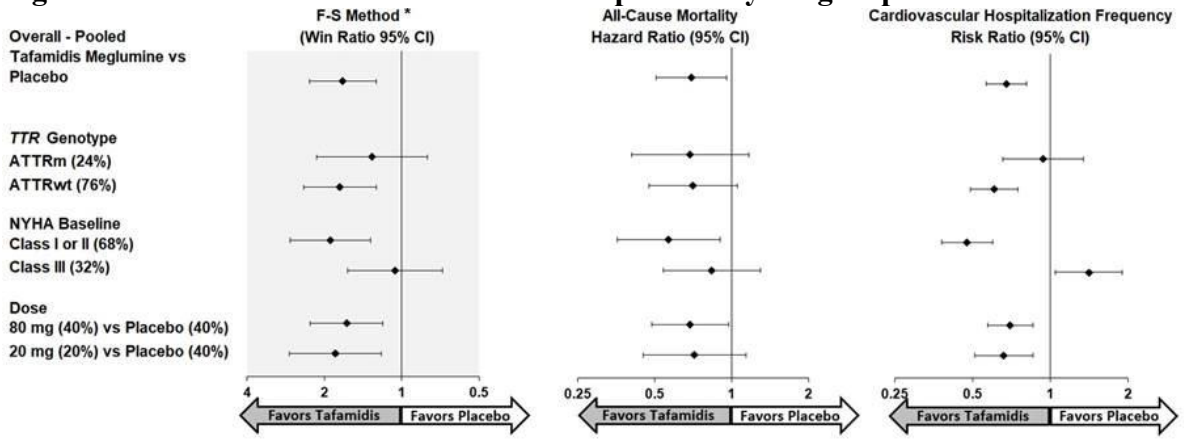
Abbreviations: 6MWT=6-Minute Walk Test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS=least squares; CI=confidence interval.

In the pivotal study, patients who exhibited >32% TTR stabilisation were considered stabilised. At Month 1, a significantly greater proportion of patients in the pooled tafamidis meglumine 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 meglumine 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) which is higher in the tafamidis meglumine group versus placebo. 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 meglumine 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.
"Tafamidis" is referring to tafamidis meglumine.

Results of the primary analysis, 6MWT at Month 30 and KCCQ-OS at Month 30 were statistically significant for both the 80 mg and 20 mg doses of tafamidis meglumine vs. placebo, with similar results for both doses.

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 20 mg tafamidis meglumine 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 20 mg tafamidis meglumine 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 numerically, but not statistically.

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

5.2 Pharmacokinetic properties

The pharmacokinetic profile of tafamidis meglumine was determined in Phase I studies in healthy volunteers and patients with ATTR-CM.

Absorption

After oral administration of VYNDAMAX once daily, the maximum peak concentration (C_{max}) is achieved at a median time (t_{max}) within 4 hours after dosing in the fasted state. Concomitant administration of a high fat, high calorie meal altered the rate of absorption, but not the extent of absorption. These results support the administration of VYNDAMAX with or without food.

Distribution

Tafamidis is highly protein bound (>99%) in plasma. The apparent steady-state volume of distribution is 18.5 litres in a 75 kg adult.

Metabolism and excretion

While 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 metabolism and excretion is likely in humans, as approximately 59% of the total administered dose is recovered in faeces mostly as unchanged drug, and approximately 22% recovered in urine mostly as the glucuronide metabolite. Based on population pharmacokinetic results, the apparent oral clearance of tafamidis meglumine is 0.228 L/h (0.263 L/h for tafamidis) and the population mean half-life is approximately 49 hours.

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.

Mean half-life and oral clearance were similar after single and repeated administration of a 20 mg dose of tafamidis meglumine, indicating a lack of induction or inhibition of tafamidis metabolism.

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

Comparative pharmacokinetics

Tafamidis 61 mg provides steady-state exposures (C_{max} and AUC) equivalent to 80 mg tafamidis meglumine (administered as four 20 mg capsules), which was administered to patients with ATTR-CM in the double-blind, placebo-controlled, randomised study (Table 7**Error! Reference source not found.**) (see Section 5.1 Pharmacodynamic properties).

Table 7: 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.h/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)

Parameter (units)	Comparison (test versus reference)	Adjusted geometric means		Test versus reference	
		Test	Reference	Ratio (%)[a] (test/reference)	90% CI[a] for ratio

Abbreviations: CI=confidence interval; mg=milligram; µg=microgram; mL=millilitre; h=hour; 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.

Special populations

Hepatic impairment

No dose adjustment is necessary in mild or moderate 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 subjects with moderate hepatic impairment (Child-Pugh Score of 7-9 inclusive) compared to healthy subjects. As TTR levels are lower in patients with moderate hepatic impairment than in healthy subjects, the exposure of tafamidis meglumine relative to the amount of TTR would be sufficient for stabilisation of the TTR tetramer in these patients. Exposure to tafamidis meglumine was similar between subjects with mild hepatic impairment and healthy subjects.

The exposure to VYNDAMAX in patients with severe hepatic impairment is unknown.

Renal impairment

VYNDAMAX has not specifically been evaluated in patients with renal impairment. Tafamidis is primarily metabolised by glucuronidation and is likely excreted via the hepatobiliary pathway. The influence of creatinine clearance on tafamidis pharmacokinetics (PK) was evaluated in a population PK analysis in patients with creatinine clearance >18 mL/min. Pharmacokinetic estimates indicated no difference in apparent oral clearance of tafamidis in patients with creatinine clearance <80 mL/min compared to those with creatinine clearance ≥80 mL/min. No dosage adjustment is required in patients with renal impairment. Limited data are available in patients with severe renal impairment (creatinine clearance ≤30 mL/min).

Elderly

Based on population pharmacokinetic results, patients ≥65 years of age had an average 15% lower estimate of apparent oral clearance at steady-state when compared with patients under the age of 65. 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

Genotoxicity

Tafamidis was not genotoxic in a bacterial reverse mutation assay, in an *in vitro* human lymphocyte chromosomal aberration assay or in an *in vivo* rat bone marrow micronucleus test. Nonclinical data demonstrated no special hazard for humans based on conventional studies of genotoxicity.

Carcinogenicity

There was no evidence of increased incidence of neoplasia in a 2-year carcinogenicity study in rats at exposures up to 18-times the human AUC at the clinical dose of 61 mg tafamidis. There was no evidence of an increased incidence of neoplasia in the transgenic (Tg)-rasH2 mouse following repeat daily administration for 26 weeks at exposures up to 9.6-times the human AUC at the clinical doses of 61 mg tafamidis. In this study, significant non-neoplastic lesions were noted in the kidneys (nephrosis) and liver (centrilobular hypertrophy and single cell necrosis) in the Tg-rasH2 mice at dose levels ≥2.8-times the clinical AUC of 61 mg tafamidis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 400

Polysorbate 20

Povidone

Butylated hydroxytoluene

Gelatin shell (117781)
- Gelatin
- Glycerol
- Iron oxide red
- Partially dehydrated liquid sorbitol
- Sorbitol
- Mannitol

Opacode WB water based monogramming ink NSP-78-18022 White (PI 3883)
- Ethanol
- Isopropyl alcohol
- Macrogol 400
- Polyvinyl acetate phthalate
- Propylene glycol
- Titanium dioxide
- Strong ammonium solution

6.2 Incompatibilities

See Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Not all presentations may be available.

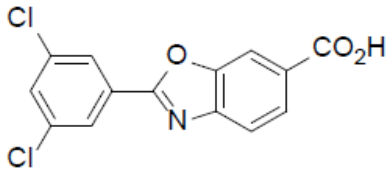
Cartons containing Aluminium/Aluminium blisters of 30 soft capsules.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure



CAS number

594839-88-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

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9. DATE OF FIRST APPROVAL

16 March 2020

10. DATE OF REVISION

15 January 2026

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of warning on interaction with BCRP substrates

Section changed	Summary of new information
4.5	Addition of other common examples of BCRP substrates and monitoring instructions when co-administering with BCRP substrates.
8	Addition of Sponsor website address
All	Minor editorial changes