Date: 23 April 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Vyndaqel

International non-proprietary name: Vyndaqel 20 mg: tafamidis meglumine, Vyndaqel 61 mg: tafamidis

Pharmaceutical form: soft capsules

Dosage strength: 20 mg and 61 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Pfizer AG

Marketing Authorisation Nos.: 67083 (20 mg) and 67518 (61 mg)

Decision and Decision date: approved on 05 March 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
ATTR	Transthyretin amyloidosis
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTR-PN	Transthyretin amyloid polyneuropathy
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
CLCR	Creatinine Clearance
CL/F	Apparent Clearance
Cmax	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
EC50	Half-maximal effective concentration
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
Kd	Dissociation constant
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MATE	Multidrug and toxin extrusion
Max	Maximum
Min	Minimum
MRP	Multidrug resistance-associated proteins
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
NT-proBNP	N-terminal prohormone brain natriuretic peptide
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PD	Pharmacodynamics
PEC	Predicted environmental concentration
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PKPD	Pharmacokinetic/pharmacodynamic
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
QD	Once daily
Q/F	Apparent inter-compartmental clearance
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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TTR	Transthyretin
TTR-CM	Transthyretin cardiomyopathy
UGT	Uridine 5'-Diphospho-Glucuronosyltransferase
V122I	Substitution of isoleucine for valine at position 122, Val122Ile
V30M	Substitution of methionine for valine at position 30, Val30Met
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution
Vss	Volume of distribution at steady state

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)
The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Status was granted on 13 September 2018.

2.2 Indication and Dosage

2.2.1 Requested Indication

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.

2.2.2 Approved Indication

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

2.2.3 Requested Dosage

Dosage:
Treatment should be initiated by, and remain under the supervision of, a physician knowledgeable in the management of patients with transthyretin amyloidosis.
Posology
The recommended dose of Vyndaqel is 61 mg tafamidis orally once daily (see section "Properties/Effects") or 80 mg tafamidis meglumine (administered as 4 x 20 mg capsules).
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 milligram basis (see sections "Properties/Effects" and "Pharmacokinetics").

Special dosage instructions

Patients with impaired hepatic function
No dosage adjustment is required for patients with mild or moderate hepatic impairment.
Vyndaqel has not been studied in patients with severe hepatic impairment.
Patients with impaired renal function
No dosage adjustment is required for patients with renal impairment.
Elderly patients
No dosage adjustment is required for elderly patients (≥ 65 years) (see section "Pharmacokinetic properties").
Children and adolescents
Vyndaqel should not be prescribed in the paediatric population as transthyretin amyloidosis is not a disease present in this population.

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2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	15 April 2019
Formal control completed	17 April 2019
List of Questions (LoQ)	20 June 2019
Answers to LoQ	1 October 2019
Predecision	20 November 2019
Answers to Predecision	22 January 2020
Labelling corrections	4 February 2020
Answers to Labelling corrections:	17 February 2020
Final Decision	05 March 2020
Decision	approval

2.4 Medical Context

ATTR-CM is a cardiac disease with deposition of TTR amyloid fibrils in different parts of the heart, causing an impaired pump function of the heart. The myocardium is a key deposition and accumulation site of TTR amyloid fibrils, which leads first to diastolic dysfunction and subsequently to cardiomyopathy and heart failure. Patients with ATTR-CM are at risk of death from different cardiac causes as sudden death, congestive heart failure, and myocardial infarction.

There exists no approved medical treatment for ATTR-CM. The treatment of symptomatic ATTR-CM has two goals: therapy of heart failure and treatment of the underlying disease.

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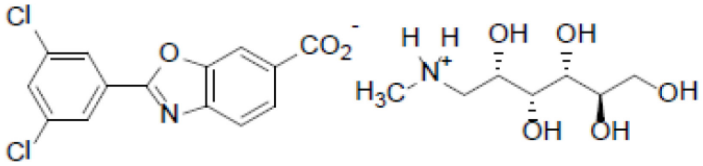
3 Quality Aspects

3.1 Drug Substance

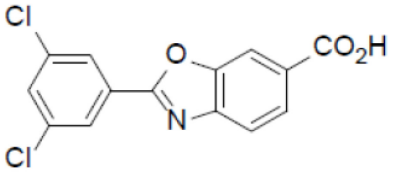
Vyndaqel 20 mg

INN: Tafamidis meglumine
Chemical name: 2-(3,5-dichlorophenyl)-benzoxazole-6-carboxylic acid mono(1-deoxy-1-methylamino-D-glucitol)
Molecular formula: $C_{14}H_7Cl_2NO_3$ $C_7H_{17}NO_5$ (Tafamidis meglumine)
$C_{14}H_7Cl_2NO_3$ (Tafamidis)
Molecular mass: 503.33 g/mol (Tafamidis meglumine)
308.12 g/mol (Tafamidis)
Molecular structure:



Tafamidis is a white to pink powder and is not hygroscopic. Tafamidis (free acid) does not have a chiral center. The meglumine salt has a D-(-) configuration. The stoichiometry is 1:1 (active pharmaceutical ingredient: counterion). Tafamidis is categorised as a Class IV drug substance (low solubility and low permeability) according to the Biopharmaceutics Classification System.
The drug substance is manufactured by multiple step chemical synthesis with final isolation by crystallisation.
The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, assay, impurities and particle size.
Appropriate stability data have been presented and justify the established re-test period.

Vyndaqel 61 mg
INN: Tafamidis
Chemical name: 2-(3,5-dichlorophenyl)-1,3-benzoxazole-6-carboxylic acid
Molecular formula: $C_{14}H_7Cl_2NO_3$
Molecular mass: 308.12 g/mol
Molecular structure:



Tafamidis is a white to pink powder, is not hygroscopic, and has no chiral center. Tafamidis is categorised as a Class IV drug substance (low solubility and low permeability) according to the Biopharmaceutics Classification System.
The drug substance is manufactured by multiple step chemical synthesis with final isolation by crystallisation. It is manufactured as the anhydrous crystalline form (Form 1).
The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, assay, impurities and particle size.
Appropriate stability data have been presented and justify the established re-test period.

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3.2 Drug Product

Vyndaqel 20 mg
The drug product is presented as immediate-release soft gelatin capsules. Each capsule contains 20 mg of tafamidis meglumine, equivalent to 12.2 mg of tafamidis as the free acid. The soft gelatin capsules are oblong, 21 mm in length, opaque yellow and printed with “VYN 20” in red.
The composition of the drug product is adequately described, qualitatively and quantitatively.
Suitable pharmaceutical development data have been provided for the finished drug product composition and manufacturing process, including establishment of the Quality Target Product Profile (QTPP), the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP).
The manufacturing process is described narratively and in sufficient detail, taking into account the pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.
Adequate validation data pertaining to the commercial manufacturing process are available.
The drug product specification covers relevant physicochemical characteristics; identification, assay and purity tests are also included. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.
The drug product is packaged into aluminium-aluminium peel/push blisters in order to provide child resistance.
Appropriate stability data have been generated in accordance with relevant international guidelines. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

Vyndaqel 61 mg
The drug product is presented as immediate-release soft gelatin capsules. Each capsule contains 61 mg of tafamidis (free acid). The soft gelatin capsules are oblong, 21 mm in length, opaque reddish brown and printed with “VYN 61” in white ink.
The composition of the drug product is adequately described, qualitatively and quantitatively.
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including establishment of the Quality Target Product Profile (QTPP), the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP).
The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.
Adequate validation data pertaining to the commercial manufacturing process are available.
The drug product specification covers relevant physicochemical characteristics; identification, assay and purity tests are also included. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.
The drug product is packaged into aluminium-aluminium peel/push blisters in order to provide child resistance.
Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

3.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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4 Nonclinical Aspects

The assessment below also considers that of the European Medicines Agency (Assessment Vyndaqel, International non-proprietary name: tafamidis meglumine, Procedure No.: EMEA/H/C/002294, 22 September 2011, EMA/729083/2011, Committee for Medicinal Products for Human Use (CHMP)).

Pharmacology

Tafamidis binds to both sites of wild-type transthyretin (TTR), with K_{d1} = 2-3 nM and K_{d2} = 154-278 nM (negative cooperativity). In human blood plasma, tafamidis binds to TTR with a stoichiometry of at least 0.81 ± 0.02, indicating selective binding to TTR over other plasma proteins. As shown in a series of in vitro experiments, binding of tafamidis stabilises the TTR tetramer against dissociation and subsequent denaturation. In the subunit exchange assay, under physiological conditions, tetramer dissociation was negligible at a tafamidis:TTR concentration ratio of 1.5, while complete exchange was observed in the absence of the stabiliser. Under acidic conditions at a physiologically relevant TTR concentration (3.6 µM), tafamidis inhibited fibril formation in a concentration-dependent manner, with similar potency for wild-type TTR or amyloidogenic mutant TTR (V30M and V122I), with EC50 values of 2.7, 3.2 and 4.1 µM, respectively (i.e. at a tafamidis:TTR stoichiometry close to 1). Under urea denaturation conditions in human plasma, tafamidis at 3.6 and/or 7.2 µM (1 to 2 µg/mL) stabilised wild-type TTR, amyloidogenic variants V30M and V122I as well as 26 other variants of TTR.

No *in vivo* primary pharmacodynamic studies were conducted with tafamidis in the absence of any established disease model of transthyretin amyloid cardiomyopathy (ATTR-CM) or transthyretin familial amyloid polyneuropathy (ATTR-PN).

No off-target activity was identified in a broad panel of receptors (including the thyroid hormone receptor), transporters and ion channels, except for binding to the δ2-opioid receptor with an IC_{50} of 8.3 µM. This was confirmed in the hamster vas deferens where tafamidis showed agonistic activity on the δ2-opioid receptor at concentrations of around 10 µM (34 and 36 times human C_{max} unbound at clinical doses of 80 mg tafamidis meglumine and 61 mg tafamidis, respectively). Tafamidis did not inhibit cyclooxygenase-1 (COX-1) or COX-2.

The single-dose safety pharmacology study did not reveal any adverse effects on central nervous system function in the rat up to the maximum dose of 100 mg/kg (exposure 18 and 19 times human C_{max} at clinical doses of 80 mg tafamidis meglumine and 61 mg tafamidis, respectively). Tafamidis did not inhibit the hERG current at concentrations up to 30 µM. However, a concentration-dependent stimulation of the hERG current was noted, reaching 10% at 30 µM (102 and 108 times human C_{max} unbound at clinical doses of 80 mg tafamidis meglumine and 61 mg tafamidis, respectively). There were no adverse effects on cardiovascular or respiratory function in the dog after single doses up to 300 mg/kg, except for a QRS prolongation and a QTc shortening at ≥100 mg/kg (exposure ≥ 22 times human C_{max} at clinical doses of 80 mg tafamidis meglumine and 61 mg tafamidis). There were no adverse effects on electrocardiograms in humans.

Pharmacokinetics

Oral bioavailability of tafamidis was close to 100% in rats and dogs. Exposure increased proportionally with the dose, but a trend to saturation was noted at higher doses. T_{max} typically ranged from 0.5 to 4 h. Accumulation was observed after repeated once daily dosing in mice, rats and rabbits, but not in dogs. Plasma half-life was approximately 29-43 h in rats and 55-62 h in dogs, which is similar to that in humans (49 h).

The volume of distribution at steady state (V_{ss}) in rats and dogs (0.3 L/kg) was similar to that in humans (about 0.2 L/kg) and corresponds to the extracellular water content. Tafamidis was widely distributed throughout the body in rats.

Plasma protein binding was high in all species including humans (97.1, 99.0, 99.1 and ≥99.2% in mice, rats, dogs and human plasma, respectively). In rats, tafamidis distributed into foetal tissues and was transferred into the milk.

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The metabolism of tafamidis in mice, rats, rabbits and dogs was not extensive. The major metabolite identified across all tested species (except for rabbits) was acylglucuronide, which is also the only metabolite in humans.

Excretion of tafamidis in rats was slow with a half-life of about 45 h. Studies in rats showed that tafamidis and its acylglucuronide metabolite are subject to enterohepatic recycling. Tafamidis was mainly excreted in faeces as unchanged tafamidis, while the acylglucuronide metabolite was excreted in urine. In humans, most of the administered dose was also recovered in the faeces.

Toxicology
The pivotal repeat-dose toxicity studies were performed in rats and dogs. The species selection is considered appropriate as the pharmacological target (i.e. TTR) is similar in humans, rats and dogs, and the only detected relevant human metabolite is also present in rats and dogs. One study was also performed in mice to select the doses for the carcinogenicity study. Tafamidis was administered orally, in line with the intended clinical route of administration.

Mortality was observed at high doses in mice (≥240 mg/kg), rats (≥ 100 mg/kg) and dogs (≥ 100 mg/kg). CNS-related clinical signs were observed in mice at ≥ 240 mg/kg and dogs at ≥ 100 mg/kg. The liver was identified as a target organ in all species. Findings included increases in liver weight, increases in transaminases and bilirubin, centrilobular hypertrophy and/or centrilobular single cell necrosis. Other target organs include the gastrointestinal tract and the kidney, but these were considered of minor toxicological relevance. The NOEL was 10 mg/kg/day (exposures in males and females 0.9 and 0.7 times the human $AUC_{0\text{-}24h}$, respectively, at clinical doses of 80 mg tafamidis meglumine and 61 mg tafamidis) in the 28-day mouse study. The NOAEL was 30 mg/kg/day (exposures in males and females 14 and 19 times the human $AUC_{0\text{-}24h}$, respectively, at the clinical dose of 80 mg tafamidis meglumine and 13 and 18 times, respectively, at the clinical dose of 61 mg tafamidis) in the 13/26-week rat study. The NOAEL was 45 mg/kg/day (exposures in males and females 8.7 and 11 times the human $AUC_{0\text{-}24h}$, respectively, at the clinical dose of 80 mg tafamidis meglumine and 8.5 and 11 times the clinical dose of 61 mg tafamidis) in the 13/39-week dog study. The low safety margins or their absences are acceptable given the severity of the disease and the current lack of therapeutic options. Hepatotoxicity is included as an important potential risk in the RMP

Tafamidis was not mutagenic in the Ames test. Polyploidy was noted in the chromosomal aberration assay at ≥ 100 µg/mL. Since polyploidy is a questionable marker for aneugenicity and the rat micronucleus test was negative, tafamidis is not considered genotoxic based on the available weight of evidence.

Tafamidis was not carcinogenic in transgenic rasH2 mice or rats.

Fertility was not impaired in the rat fertility and early embryonic development study (NOAEL 30 mg/kg/day, exposure in males 12 times and in females 9.7 and 9.5 times human $AUC_{0\text{-}24h}$ at clinical doses of 80 mg tafamidis meglumine and 61 mg tafamidis, respectively). The embryo-foetal development study in the rat revealed maternal toxicity at 45 mg/kg/day and embryo-foetal toxicity at ≥ 15 mg/kg/day, but no teratogenicity. The maternal NOAEL was 30 mg/kg/day (exposure 9.7 and 9.5 times human $AUC_{0\text{-}24h}$ at clinical doses of 80 mg tafamidis meglumine and 61 mg tafamidis, respectively) and the embryo-foetal NOAEL 15 mg/kg/day (exposure 6.6 and 6.4 times human $AUC_{0\text{-}24h}$ at clinical doses of 80 mg tafamidis meglumine and 61 mg tafamidis, respectively). In the rabbit, maternal and embryo-foetal toxicity with teratogenicity occurred at ≥2 mg/kg/day. The maternal and embryo-foetal NOAEL was 0.5 mg/kg/day (exposure 0.9 times human $AUC_{0\text{-}24h}$). The rat pre- and postnatal development study showed maternal toxicity at ≥15 mg/kg/day. All pups died at 30 mg/kg/day, and reduced pup weights were noted at 15 mg/kg/day. Decreased foetal weights in males were associated with delayed sexual maturation. Performance in a water-maze test for learning and memory was impaired at 15 mg/kg/day. The NOAEL for maternal toxicity and development of the offspring was 5 mg/kg/day (exposure 3 times human $AUC_{0\text{-}24h}$). Since tafamidis showed embryo-foetal toxicity in both the rat and rabbit, and teratogenicity in the rabbit, it should not be used during pregnancy.

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Tafamidis did not affect T-cell dependent antibody response in mice at doses up to 120 mg/kg/day (exposure 8.3 and 8.1 times human $AUC_{0\text{-}24h}$ at clinical doses of 80 mg tafamidis meglumine and 61 mg tafamidis, respectively).

Tafamidis was not phototoxic *in vivo* in rats.

The specified impurities in the drug substance and drug product are acceptable from a nonclinical perspective. The $PEC_{SURFACE\ WATER}$ value is around the action limit of 0.01 µg/L. A Phase II Tier A environmental fate and effects analysis, and an updated ERA were requested as post-approval commitment.

All relevant nonclinical safety findings are included in the RMP.

Nonclinical conclusions
The submitted nonclinical documentation is considered to be adequate to support the approval of tafamidis (meglumine salt and free acid) for the proposed indication. All safety-relevant nonclinical data are included in the information for healthcare professionals.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

ADME
Absorption and biopharmaceutical Development
The proposed dose for the current indication of treatment of symptomatic transthyretin (TTR) amyloid cardiomyopathy (ATTR-CM) is 80 mg (=> 4x20 mg) tafamidis meglumine once daily (QD). In order to administer the higher dose for the treatment of ATTR-CM with a single capsule, a capsule containing tafamidis as free acid was developed. Concentration-dependent gelling did not permit the development of a tafamidis meglumine 80 mg single capsule.

The main formulations of tafamidis meglumine employed during clinical development were:

The Phase 2/3 capsule using non-micronised tafamidis meglumine.

The Phase 2/3 capsule using micronised tafamidis meglumine.

The commercial formulation using micronised tafamidis meglumine.

All these capsules contained 20 mg tafamidis meglumine.

The Phase 2/3 capsules containing micronised tafamidis meglumine were both administered in the pivotal clinical safety and efficacy studies for the current indication. Bioequivalence was demonstrated between these two capsules containing micronised drug material. No direct comparison of the capsules containing micronised and non-micronised tafamidis meglumine is available.

After fasted single dose administration of 61 mg of the proposed commercial tafamidis free acid capsule and 80 mg (4x20 mg) of the commercial tafamidis meglumine capsule, bioequivalence was demonstrated for tafamidis AUC. Cmax was 20.3% lower after administration of the free acid capsule.

The pivotal bioequivalence study compared 80 mg (4x20 mg) of the commercial tafamidis meglumine capsule and 61 mg of the commercial tafamidis free acid capsule after multiple dosing (fasted). After multiple dosing, bioequivalence could be demonstrated for both Cmax and AUC.

A high fat, high calorie meal had no impact on the tafamidis AUC after administration of both formulations. After fed administration, Cmax was 32.4% higher compared to fasted administration for the 61 mg free acid capsule and 14.5% lower for 80 mg (4x20 mg) tafamidis meglumine. The median tmax was 4 h and 3 h for fasted and fed administration of 61 mg tafamidis free acid, respectively. For 80 mg (4x20 mg) or tafamidis meglumine, it was 1.5 h after fasted administration and 3 h after fed administration, respectively.

The recommendation to take both tafamidis formulations independently of food intake is supported by the available pharmacokinetic data.

Dose Proportionality
The tafamidis exposure (both Cmax and AUC) generally increased slightly less than dose proportionally after both single (up to 480 mg) and multiple dosing (up to 80 mg QD), independent of the administered formulation.

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Pharmacokinetics after Multiple Dosing
After QD dosing for 14 days, steady state was reached on Day 9. A 2.1- to 2.7-fold accumulation was observed.

Distribution
The tafamidis mean fraction unbound was 0.008. The Vss values for tafamidis meglumine and tafamidis are 16 L and 18.5 L, respectively.

Metabolism
In vitro Data
Tafamidis was not metabolised by hepatic CYPs, but conjugated by several uridine 5'-diphospho-glucuronosyltransferases (UGTs). UGT 1A1, 1A3, 1A6, 1A7, 1A8, 1A9 and 2B7 were involved in the formation of the tafamidis acylglucuronide metabolite.

Clinical Data
After administration of a ^{14}C-labelled single dose of tafamidis, unchanged tafamidis was the major component in plasma. This finding was confirmed by “cold” metabolite profiling: Tafamidis accounted for more than 95% of all the detected analytes in plasma. The only other metabolite in plasma, accounting for about 3.5%, was the acylglucuronide.

Elimination
After administration of a ^{14}C-labelled single dose of tafamidis, 22.35% and 58.5% of the total radioactivity were excreted in urine and faeces, respectively. The tafamidis half-life was about 49 hours.

Special Populations
The impact of mild or moderate hepatic impairment on the pharmacokinetics of tafamidis was investigated in a dedicated Phase 1 study. The study did not include subjects with severe hepatic impairment.

Tafamidis Cmax was similar in subjects with mild hepatic impairment and normal hepatic function, while AUClast and AUCinf were 16% and 17% lower, respectively. Tafamidis Cmax was similar in subjects with moderate hepatic impairment and normal hepatic function, while AUClast and AUCinf were 36% and 41% lower, respectively. The dosing recommendations for patients with impaired hepatic function presented in the product information are supported by the pharmacokinetic data.

The potential impact of other intrinsic factors like weight, gender, hepatic function, renal function on tafamidis PK was investigated in a pop PK analysis including 17 Phase 1 studies, two Phase 2 studies, two Phase 2/3 studies and two Phase 3 studies. The pop PK dataset included mainly healthy subject data (43.8% of the total population) as well as 135 (17.8%) ATTR-PN patients and 292 (38.4%) ATTR-CM patients.

The only subjects with mild or moderate hepatic impairment included in the pop PK dataset (n=9 each) were the participants of the Phase 1 hepatic impairment study. The vast majority of the subjects/patients in the dataset (n=742, 97.6%) had normal hepatic function.
The dataset included 406 (53.4%), 148 (19.5%), 188 (24.7%) and 18 (2.4%) of patients with normal renal function, mild, moderate or severe renal impairment, respectively.
It also included 471 (62.0%), 128 (16.8%) and 161 (21.2%) of patients < 65 years, ≥ 65 and < 75 years and ≥ 75 years of age, respectively. The range of the continuous covariates was sufficiently wide to detect a potential impact on tafamidis PK.

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In addition, several factors to account for the differences of the absorption rate of the various formulations administered in the included studies, the final pop PK model included the following covariate relationships:

Body weight as a covariate of CL/F, Q/F, Vc/F and Vp/F
Age as a categorical covariate (> and < 65 years) on CL/F
Moderate hepatic impairment as a covariate of CL/F
Patient status as a covariate of bioavailability.

The final pop PK model described the tafamidis concentration versus time profiles reasonably well.

Of all these statistically significant covariates, moderate hepatic impairment had the greatest impact on tafamidis exposure. For AUC, the results of the pop PK analyses were in good agreement with the results of the corresponding Phase 1 study.

Renal function, also investigated as a categorical covariate (CLCR < 80 mL/min and ≥ 80 mL/min), had no statistically significant impact on tafamidis CL/F in the formal covariate analysis. The tafamidis AUC was similar in subjects with CLCR < 80 mL/min and ≥ 80 mL/min.

The results of the pop PK analysis support the dosing recommendations for elderly patients and patients with renal impairment.

Interactions

Impact of tafamidis on other drugs
Based on in vitro data, tafamidis is unlikely to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 in vivo at therapeutic exposure after administration of 61 mg tafamidis free acid QD.
In vivo induction of CYP2B6 and 3A4 cannot be excluded at a therapeutic tafamidis exposure, but in vivo induction of CYP1A2 is unlikely.

Regarding transporters, the in vitro data indicate that an in vivo inhibition of BCRP, OAT1 and OAT3 at a therapeutic exposure cannot be excluded. The risk of an in vivo inhibition of P-gp, OCT2, MATE1, MATE2K, OATP1B1 and OATP1B3 appears to be low.

Furthermore, the in vivo inhibition of intestinal UGT1A1 cannot be excluded based on the available in vitro data. The in vivo inhibition of UGT1A4, 1A6, 1A9 and 2B7 is unlikely.

As the in vitro data indicated a potential to induce CYP4A4 (and, even more likely, 2B6), a midazolam interaction study was conducted. In this study, 20 mg tafamidis QD for 14 days had no impact on the exposure of midazolam or 1-OH midazolam. The tafamidis exposure observed in this study was considerably lower than the exposure after 80/61 mg QD. This point was the subject of discussion with the applicant. Considering the totality of available data, an in vivo induction at 61/80 mg tafamidis appears unlikely, but cannot be completely excluded. As a consequence of this discussion, a clear description of the tafamidis dose employed in the interaction study was included in the product information.

Impact of other drugs on tafamidis
The potential impact of a UGT inhibitor or any other drugs on tafamidis PK is unknown. No clinical interaction studies investigating the potential impact of other drugs on tafamidis were conducted.

The inclusion of specific dosing recommendations or warnings regarding the interaction potential of tafamidis was not deemed necessary, but the product information contains a clear description of the available in vitro and clinical data and the associated potential risks.

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Pharmacodynamics
After administration of a single 400 mg dose as oral solution, tafamidis had no effect on QTcF or heart rate. Assay sensitivity was demonstrated with moxifloxacin.

The tafamidis mean Cmax values achieved in the tQT study were 2.2- to 2.4-fold higher compared to Cmax after multiple dosing of 61 mg tafamidis free acid or 80 mg tafamidis meglumine in healthy subjects.

5.2 Dose Finding and Dose Recommendation

A dose finding study was not carried out.

Doses of 80 mg and 20 mg tafamidis were selected for the submitted pivotal clinical study, based on the results of pharmacodynamic studies assessing the relationship between TTR stabilisation and molar ratio of tafamidis.

5.3 Efficacy

The efficacy of tafamidis 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 either to 20 mg (n = 88) or 80 mg (n = 176) tafamidis or equivalent placebo (n = 177) in addition to standard heart failure treatment for 30 months. The treatment allocation was stratified by TTR genotype and NYHA class. Patients with a heart transplant were excluded from the study. Overall, the baseline data of the tafamidis and placebo groups were comparable.
Primary analysis using the Finkelstein-Schoenfeld method was performed in hierarchical combination to overall mortality and frequency of cardiovascular-related hospitalisations. The analysis showed a significant reduction (p = 0.0006) in all-cause mortality and frequency of cardiovascular hospitalisations in the pooled tafamidis dose groups (20 mg and 80 mg) compared to placebo. The analysis of the individual components of the primary endpoint (all-cause mortality and cardiovascular-related hospitalisations) also showed significant reductions in the tafamidis groups compared to placebo. The hazard ratio for all-cause mortality was 0.698 (95% CI 0.508, 0.958) for both tafamidis doses compared to placebo (p = 0.0259).
The treatment effect of tafamidis on functional capacity and health status was assessed using the 6- minute walk test (6MWT) or Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ OS) score. A significant treatment effect in favour of both tafamidis doses was observed after 6 months and was maintained until month 30 both in terms of the distance in the 6MWT and the score for KCCQ OS. Biomarkers associated with heart failure (NT-proBNP and troponin I) favoured tafamidis over placebo.

Further results are given in the information for healthcare professionals, section “Clinical efficacy”.

5.4 Safety

In the pivotal clinical trial, the discontinuation rates were low overall, irrespective of the treatment arm or tafamidis dose. The frequency of adverse effects in patients treated with 20 mg or 80 mg tafamidis was similar and comparable to placebo. None of the adverse effects were classified as adverse drug effects associated with the use of tafamidis in this population. The safety profiles of the 20 mg and 80 mg tafamidis doses were comparable in patients with ATTR-CM.
The acceptable safety and tolerability of tafamidis in patients with ATTR-CM was also supported by safety data from the ATTR-PN population, in which 137 ATTR-PN patients were examined in clinical trials with an average exposure of 44.2 months.

Further details concerning safety are given in the information for healthcare professionals section “Undesirable effects”.

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5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Tafamidis is the first oral drug for the treatment of ATTR-CM.
The submitted phase 3 trial demonstrated a reduction of all-cause mortality and cardiovascular-related hospitalisations in selected patients with ATTR-CM.
Safety results indicated that both dosages of tafamidis, 20 mg and 80 mg once daily, were well tolerated.

Overall, the benefit-risk ratio for tafamidis 80 mg once daily for the treatment of ATTR-CM has been assessed to be positive.

Tafamidis should be administered by physicians experienced in amyloidosis therapy.

Clinical Pharmacology – Beneficial Effects
Tafamidis can be administered independently of meals. Apart from a slightly less than dose proportional increase of exposure due to its limited solubility, tafamidis PK is linear. No dose adjustments are required in mild or moderate hepatic impairment, renal impairment of all degrees or elderly patients.

Tafamidis is unlikely to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 in vivo at therapeutic exposure. It had no effect on midazolam exposure in a clinical interaction study. Tafamidis is not a substrate of P-gp, MRP2, OATP1B1 or OATP1B3. In vivo inhibition of P-gp, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2K is unlikely.
Tafamidis had no effect on QTcF or heart rate at supratherapeutic exposure.

Clinical Pharmacology – Uncertainties related to the Beneficial Effects
The impact of proton-pump inhibitors or other antacids on the absorption of tafamidis is unknown, but the risk of major interactions appears low.
The assessment of dose proportionality is largely based on oral solution data. The problem is attenuated by the fact that only one dose per formulation is applied for.
The metabolism of tafamidis has not been fully characterised. However, glucuronidation has been observed and unchanged tafamidis is the main compound in plasma**.**
There are no data available on subjects with severe hepatic impairment. This point is appropriately addressed in the information for healthcare professionals.
A dose of 20 mg tafamidis meglumine QD was used in the midazolam interaction study. Thus, the effect of tafamidis after 80/61 mg QD on midazolam is unknown. The tafamidis dose used in the interaction study is indicated in the corresponding section of the information for healthcare professionals.
No data are available regarding the impact of other drugs (for example UGT inhibitors) on tafamidis PK. This point is appropriately addressed in the information for healthcare professionals.

Clinical Pharmacology – Unfavourable Effects
Tafamidis meglumine and tafamidis free acid are not bioequivalent on a mg basis, i.e. different doses are required to achieve comparable tafamidis exposure.
The possibility to inhibit BCRP, OAT1, OAT3 and intestinal UTG1A1 in vivo is appropriately addressed in the information for healthcare professionals. A clinical interaction study with rosuvastatin (BCRP substrate) is planned.

Conclusion Clinical Pharmacology
Overall, the PK and PKPD profile of tafamidis does not raise any major concerns.

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5.6 Approved Indication and Dosage

See Information for healthcare professionals in the Appendix.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Vyndaqel was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Vyndaqel

Composition

Active substances

Soft capsules 20 mg: Tafamidis meglumine.

Soft capsules 61 mg: Tafamidis.

Excipients

Soft capsules 20 mg: Brilliant blue FCF, carmine, gelatin, glycerol, yellow iron oxide, macrogol 400, polysorbate 80, polyvinyl acetate phthalate, propylene glycol, sorbitan monooleate, sorbitol liquid partially dehydrated corresp. sorbitol (E 420, max. 44 mg), titanium dioxide.

Soft capsules 61 mg: Butylated hydroxytoluene, gelatine, glycerol, red iron oxide, macrogol 400, polysorbate 20, polyvinyl acetate phthalate, povidone (K-value 90), propylene glycol, sorbitol liquid partially dehydrated corresp. sorbitol (E 420, max. 44 mg), titanium dioxide.

Pharmaceutical form and active substance quantity per unit

Soft capsules.

Soft capsule 20 mg: 1 soft capsule contains 20 mg of micronized tafamidis meglumine (equivalent to 12.2 mg tafamidis). Yellow, opaque, oblong (approximately 21 mm) capsule printed with «VYN 20» in red.

Soft capsule 61 mg: 1 soft capsule contains 61 mg micronized tafamidis. Reddish brown, opaque, oblong (approximately 21 mm) capsule printed with «VYN 61» in white.

Indications/Uses

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.

Dosage/Administration

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

The recommended dose of Vyndaqel is 61 mg tafamidis orally once daily (see section «Properties/Effects») or 80 mg tafamidis meglumine (administered as 4x20 mg capsules).

At the discretion of the treating physician, the dose may be reduced to 20 mg tafamidis meglumine, if not tolerated.

Tafamidis and tafamidis meglumine are not interchangeable on a per milligram basis. 61 mg tafamidis is bioequivalent to 80 mg tafamidis meglumine. Please refer to section «Properties/Effects» and «Pharmacokinetic properties» for more information on the bioequivalence.

Special dosage instructions

Patients with impaired hepatic function

No dosage adjustment is required for patients with mild or moderate hepatic impairment. Vyndaqel has not been studied in patients with severe hepatic impairment and caution is recommended.

Patients with impaired renal function

No dosage adjustment is required for patients with renal impairment. Limited data are available in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min).

Elderly patients

No dosage adjustment is required for elderly patients (≥65 years) (see section «Pharmacokinetic properties»).

Children and adolescents

Vyndaqel should not be prescribed in the pediatric population as the use and safety has not been studied and transthyretin amyloidosis is not a disease present in this population.

Delayed administration

If a dose is missed, the patient should take the dose as soon as remembered. If less than 6 hours remain until 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.

Mode of administration

Oral use.

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients of Vyndaqel.

Warnings and precautions

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

This medicinal product contains 44 mg sorbitol (E 420) 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 sorbitol content in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Interactions

In vitro studies

Tafamidis induces CYP2B6 and CYP3A4 and does not induce CYP1A2. Tafamidis does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5 or CYP2D6.

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 (breast cancer resistant protein) and may increase systemic exposure of substrates of this transporter (e.g. methotrexate, rosuvastatin, imatinib) following 80 mg tafamidis meglumine daily dose, and 61 mg tafamidis daily dose.

Tafamidis may have the potential to inhibit organic anion transporter 1 (OAT1) and OAT3 and may cause drug-drug interactions with substrates of this transporters (e.g., non-steroidal anti-inflammatory drugs, bumetanide [not authorised in Switzerland], furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine [not authorised in Switzerland]).

Effect of Vyndaqel on other medicinal products

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.

Effect of other medicinal products on Vyndaqel

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

Other interactions

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.

Pregnancy, lactation

Women of childbearing potential

Contraceptive measures should be used by women of childbearing potential during treatment with Vyndaqel, and, due to the prolonged half-life, for 1 month after stopping treatment.

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

Pregnancy

Insufficient data available on use in pregnant patients.

Animal studies showed reproductive toxicity (see «Preclinical data» section).

The potential risk for humans is unknown. Vyndaqel should not be administered during pregnancy. To monitor outcomes of pregnant women exposed to Vyndaqel, a Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) program has been established. If a pregnancy occurs in a woman being treated with Vyndaqel, medical or healthcare professionals are encouraged to report the pregnancy to the Marketing Authorisation Holder.

Lactation

The effect of Vyndaqel on nursing infants after administration to the mother has not been studied. Animal studies have shown that tafamidis is excreted in human milk (see «Preclinical data» section). There are no clinical data available to support the presence of tafamidis in human breast milk. A risk for the newborn/child cannot be excluded. Vyndaqel should not be used during lactation.

Fertility

There were no effects of tafamidis on fertility, reproductive performance or mating behavior in the rat at any of the tested doses (see section «Preclinical data»).

Effects on ability to drive and use machines

No corresponding studies have been performed.

Undesirable effects

The data across clinical trials reflect exposure of 377 ATTR-CM (Transthyretin Amyloid Cardiomyopathy) 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). 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.

Undesirable effects were assessed from ATTR-CM clinical trials with Vyndaqel including a 30-month placebo-controlled trial in patients diagnosed with ATTR-CM (see section «Properties/Effects»). The frequency of undesirable effects in patients treated with 20 mg or 80 mg tafamidis meglumine was similar and comparable to placebo. No undesirable effects were identified as an adverse drug reaction associated with Vyndaqel administration in this population.

A lower proportion of Vyndaqel-treated patients compared to placebo discontinued due to an adverse event in the 30-month placebo-controlled trial in patients diagnosed with ATTR-CM: [40 (22.7%), 16 (18.2%), and 51 (28.8%) from the 80 mg (administered as four 20 mg capsules) of tafamidis meglumine, 20 mg tafamidis meglumine, and placebo groups, respectively].

In another Phase-III, double-blind, placebo-controlled study (Fx-005) in patients with a peripheral manifestation of transthyretin amyloidosis (N=128) treated with 20 mg tafamidis meglumine, adverse reactions reported below for Vyndaqel reflect the rates at which they occurred. Within the frequency group, adverse reactions are presented in order of decreasing frequency. Frequencies are defined as: «very common» (≥1/10).

Infections and infestations

Very common: Urinary tract infection (23%), vaginal infection (12%).

Gastrointestinal disorders

Very common: Diarrhoea (26%), upper abdominal pain (12%).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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.

Properties/Effects

ATC code

N07XX08

Mechanism of action

Tafamidis meglumine is a selective stabilizer 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 Vyndaqel to reduce all-cause mortality and cardiovascular-related hospitalization in ATTR-CM patients.

Pharmacodynamics

A TTR stabilization assay was utilized as a pharmacodynamic marker and assessed the stability of the TTR tetramer under denaturation conditions.

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

Cardiac Electrophysiology

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

Clinical efficacy

ATTR-CM

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

Patients were randomized to either tafamidis meglumine 20 mg (n=88) or 80 mg [administered as four 20 mg tafamidis meglumine capsules] (n=176) or matching placebo (n=177) once daily, in addition to standard of care (e.g., diuretics) for 30 months. Treatment assignment was stratified by the presence

or absence of a variant TTR genotype 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, 20 mg and 80 mg dose 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)
S*ex — 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)

Abbreviation: ATTRm = variant transthyretin amyloid, ATTRwt = wild type transthyretin amyloid

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

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

Primary Analysis	*Pooled Tafamidis, 20 mg and 80 mg dose n=264*	*Placebo n=177*
Number (%) of subjects alive* at Month 30	186 (70.5)	101 (57.1)
Average cardiovascular-related hospitalizations during 30 months (per patient per year) among those alive at Month 30†	0.297	0.455
p-value from F-S method	0.0006	

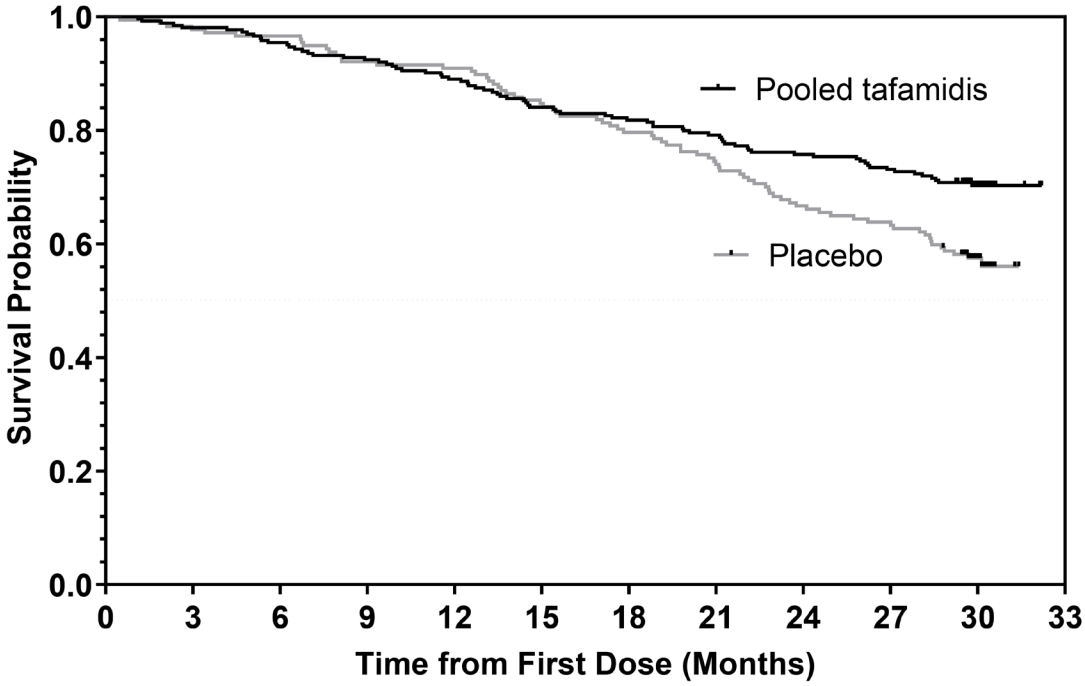
* Heart transplantation and cardiac mechanical assist device implantation are considered indicators of approaching end stage. As such, these subjects are treated in the analysis as equivalent to death. Therefore,

such subjects are not included in the count of «Number of subjects alive at Month 30» even if such subjects are alive based on 30 month vital status follow-up assessment.
† Descriptive mean among those who survived the 30 months.

Analysis of the individual components of the primary analysis (all-cause mortality and cardiovascular-related hospitalization) 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 tafamidis	264 0	259 5	252 12	244 20	235 29	222 42	216 48	209 55	200 64	193 71	99 78	0 78
Placebo	177 0	173 4	171 6	163 14	161 16	150 27	141 36	131 46	118 59	113 64	51 75	0 76

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

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

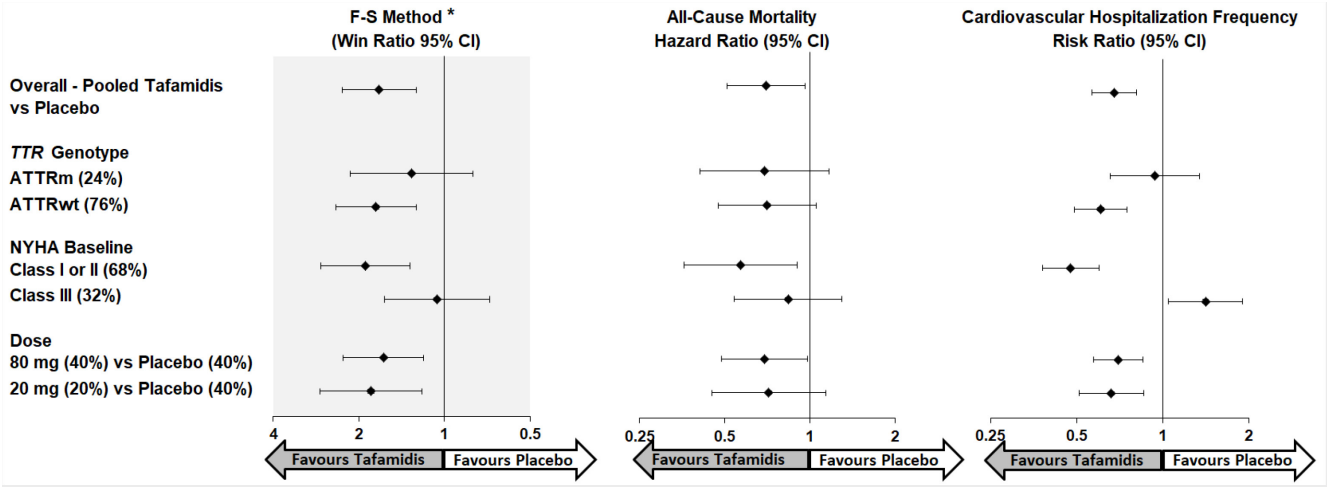
Table 3: Cardiovascular-related hospitalization frequency

	Pooled Tafamidis, 20 mg and 80 mg dose n=264	*Placebo n=177*
Total (%) number of subjects with cardiovascular-related hospitalizations	138 (52.3)	107 (60.5)
Cardiovascular-related hospitalizations per year*	0.4750	0.7025
Pooled tafamidis versus placebo treatment difference (relative risk ratio)*	0.6761	
p-value*	<0.0001	

Abbreviation: NYHA = New York Heart Association; CV = cardiovascular
* This analysis was based on a Poisson regression model with treatment, TTR genotype (variant and wild type), 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.

Results from F-S method represented by win ratio for the combined endpoint and its components (all-cause mortality and frequency of cardiovascular-related hospitalization) favored tafamidis versus placebo in the following subgroups (wild type, variant and NYHA Class I & II) except for cardiovascular-related hospitalization frequency in NYHA Class III patients (Figure 2).

Figure 2: Results from F-S Method and Components by Subgroup and Dose



Abbreviation: ATTRm = variant transthyretin amyloid, ATTRwt = wild type transthyretin amyloid, F-S = Finkelstein Schoenfeld, CI = Confidence Interval.
*F-S results presented using win ratio (based on all-cause mortality and frequency of cardiovascular hospitalization)
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-related hospitalizations for both the 20 mg and the 80 mg doses compared to placebo (p=0.0048 and p=0.0030, respectively).

The treatment effect on secondary endpoints of tafamidis on functional capacity and health status was assessed by the 6-Minute Walk Test (6MWT) and the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score, respectively.

A significant treatment effect favoring tafamidis was first observed at Month 6 and remained consistent through Month 30 on both 6MWT distance and KCCQ-OS score. Biomarkers associated with heart failure (NT-proBNP and Troponin I) favoured Vyndaqel over placebo.

Pharmacokinetics

The pharmacokinetic profile of Vyndaqel was determined in Phase I studies in healthy volunteers and patients with ATTR-PN or ATTR-CM.

Absorption

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

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, randomized study (Table 4) (see section «Properties/Effects»).

Table 4: Comparative pharmacokinetics of tafamidis 61 mg capsule to tafamidis meglumine 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; 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.

Distribution

Tafamidis is highly protein bound (>99%) in plasma. The apparent steady-state volume of distribution of tafamidis meglumine is 16 liters and 18.5 liters for tafamidis.

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.

Metabolism

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

Elimination

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. The degree of drug accumulation at steady state after repeated tafamidis daily dosing is approximately 2.5-fold greater than that observed after a single dose.
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 was achieved by Day 14.

Linearity/non-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 per day. In general, increases were proportional or slightly less than proportional to dose.

Kinetics in specific patient groups

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 Vyndaqel relative to the amount of TTR would be sufficient for stabilization of the TTR tetramer in these patients. Exposure to Vyndaqel was similar between subjects with mild hepatic impairment and healthy subjects.

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

Renal impairment

Vyndaqel has not specifically been evaluated in patients with renal impairment. Tafamidis is primarily metabolized 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 patients

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.

Preclinical data

Nonclinical data demonstrated no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity in rats and dogs, fertility and early embryonic development, genotoxicity, and carcinogenic potential.

In repeat dose toxicity and carcinogenicity studies the liver and/or kidney appeared as target organs for toxicity in mice and rats. Liver effects were observed at exposures approximately ≥0.7-times the human AUC at the clinical doses of 61 mg tafamidis and 80 mg tafamidis meglumine (see also below «Carcinogenicity»).

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 doses of 61 mg tafamidis, and 80 mg tafamidis meglumine, respectively. Non-neoplastic lesions in the liver (including centrilobular hypertrophy and necrosis) were observed at exposures approximately ≥3.4 times the human AUC at the clinical doses of 61 mg tafamidis and 80 mg tafamidis meglumine.

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, and 9.9-times the human AUC at the clinical doses of 61 mg tafamidis, and 80 mg tafamidis meglumine. 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,and ≥2.9-times the human AUC at the clinical doses of 61 mg tafamidis, and 80 mg tafamidis meglumine.

Reproductive toxicity

Fertility

There were no effects of tafamidis on fertility, reproductive performance, or mating behavior in the rat at any tested dose. Rats were dosed daily (5, 15, and 30 mg/kg/day) with tafamidis 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). Because no reproductive effects occurred at the highest dose tested, the paternal and maternal NOEL (no observed effect level) for reproductive toxicity of tafamidis is greater than 30 mg/kg/day (human equivalent dose of tafamidis greater than 4.8 mg/kg/day) and is greater than 5.5-times, and 6.9-times the clinical doses of 61 mg tafamidis, and 80 mg tafamidis meglumine.

Developmental toxicity

In an embryo-fetal developmental toxicity study in rabbits, oral administration of tafamidis (0.5, 2, or 8 mg/kg/day) from Gestation Day 7 through 19 resulted in a slight increase in skeletal variations at ≥2 mg/kg/day (approximately ≥2.1-times, and ≥2.2-times the human AUC at steady state at the clinical doses of 61 mg tafamidis and 80 mg tafamidis meglumine). Skeletal malformations, reduced embryo-fetal survival and reduction in fetal body weights were observed at 8 mg/kg/day (approximately 9.1-times and 9.3-times the human AUC at steady state at the clinical doses of 61 mg tafamidis and 80 mg tafamidis meglumine, respectively). In an embryo-fetal development toxicity study in rats, oral administration of tafamidis (15, 30, or 45 mg/kg/day) from Gestation Day 7 through 17 resulted in decreased fetal weights with no effects on fetal morphology at ≥30 mg/kg/day (approximately ≥9.5-times and ≥9.7-times the human AUC at the clinical doses of 61 mg tafamidis and 80 mg tafamidis meglumine.

In the rat pre- and postnatal development study, pregnant rats were orally administered tafamidis at doses of 5, 15, or 30 mg/kg/day from Gestation Day 7 through Lactation Day 20. Decreased pup survival and reduced pup weights were noted 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 (no observable adverse effect level) 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 0.92-times the clinical dose of 61 mg tafamidis, and approximately 1.2-times the clinical dose of 80 mg tafamidis meglumine. Tafamidis has been shown to be excreted in the milk of lactating rats.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Special precautions for storage

Do not store above 25 °C.

Keep out of the reach of children.

Instructions for handling

Any unused product should be disposed of properly.

Authorisation number

67083, 67518 (Swissmedic).

Packs

Soft capsules 20 mg: 30. [B]

Soft capsules 61 mg: 30. [B]

Marketing authorisation holder

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