1 NAME OF THE MEDICINAL PRODUCT

Vyndaqel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 20 mg of micronized tafamidis meglumine equivalent to 12.2 mg tafamidis.
Excipient with known effect

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule.

Oblong, opaque yellow soft gelatin capsule filled with a white to pink suspension and printed with "VYN 20" in red

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

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

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

Special populations

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

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

Paediatric population

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

Method of administration

Oral use.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

In vitro Tafamidis inhibits the efflux transporter BCRP (breast cancer resistant protein) with IC50=1.16 µM and may cause drug-drug interactions at clinically relevant concentrations with substrates of this transporter (e.g. methotrexate, rosuvastatin, imatinib) 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. Likewise, tafamidis inhibits the uptake transporters OAT1 and OAT3 (organic anion transporters) with IC50=2.9 µM and IC50=2.36 µM, respectively, and may cause drug-drug interactions at clinically relevant concentrations with substrates of these transporters (e.g. non-steroidal anti-inflammatory drugs, bumetanide, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine).

Based on *in vitro* data, the maximal predicted changes in AUC of OAT1 and OAT3 substrates were determined to be less than 1.25 for the tafamidis meglumine 20 mg dose, therefore, inhibition of OAT1 or OAT3 transporters by tafamidis is not expected to result in clinically significant interactions.

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

Laboratory test abnormality

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

4.6 Fertility, pregnancy and lactation

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

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated list of adverse reactions

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/ (.

4.9 Overdose

Symptoms

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

5 PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code N07XX08

Mechanism of action

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

Pharmacodynamic effect

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

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

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

Clinical efficacy and safety

The pivotal study of tafamidis meglumine in stage 1 ATTR-PN patients was an 18-month, multicentr, randomised, double-blind, placebo-controlled study. The study evaluated the safety and efficacy of once-daily 20 mg tafamidis meglumine in 128 patients with ATTR-PN with the V30M mutation and primarily stage 1 disease; 126 of the 128 patients did not routinely require assistance with ambulation. The primary outcome measures were the Neuropathy Impairment Score of the Lower Limb (NIS-LL – a physician assessment of the neurologic exam of the lower limbs) and the Norfolk Quality of Life - Diabetic Neuropathy (Norfolk QOL-DN – a patient reported outcome, total quality of life score [TQOL]). Other outcome measures included composite scores of large nerve fibre (nerve conduction, vibration threshold and heart rate response to deep breathing - HRDB) and small nerve fibre function (heat pain and cooling threshold and HRDB) and nutritional assessments utilizing the modified body mass index (mBMI – BMI multiplied by serum albumin in g/L). Eighty-six of the 91 patients completing the 18 month treatment period subsequently enrolled in an open-label extension study, where they all received once daily 20 mg tafamidis meglumine for an additional 12 months.

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

Vyndaqel versus Placebo: NIS-LL and TQOL at Month 18 (Study Fx-005)		
	Placebo	**Vyndaqel**
Pre-specified ITT Analysis	**N=61**	**N=64**
NIS-LL Responders (% Patients)	29.5%	45.3%
Difference (Vyndaqel minus Placebo)	15.8%	
95% CI of Difference (p-value)	-0.9%, 32.5% (0.068)	
TQOL Change from Baseline LSMean (SE)	7.2 (2.36)	2.0 (2.31)
Difference in LSMeans (SE)	-5.2 (3.31)	
95% CI of Difference (p-value)	-11.8, 1.3 (0.116)	
Pre-specified Efficacy Evaluable Analysis	**N=42**	**N=45**
NIS-LL Responders (% Patients)	38.1%	60.0%
Difference (Vyndaqel minus Placebo)	21.9%	
95% CI of Difference (p-value)	1.4%, 42.4% (0.041)	
TQOL Change from Baseline LSMean (SE)	8.9 (3.08)	0.1 (2.98)
Difference in LSMeans (SE)	-8.8 (4.32)	
95% CI of Difference (p-value)	-17.4, -0.2 (0.045)	
In the pre-specified ITT NIS-LL Responder analysis, patients who discontinued prior to the 18-month time point due to liver transplantation were categorized as non-responders. The pre-specified Efficacy Evaluable analysis used observed data for those patients who completed the 18 month treatment per protocol.		

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

Secondary Endpoints Changes from Baseline to Month 18 LSMean (Standard Error) (Intent to-Treat Population) (Study Fx-005)				
	Placebo N=61	Vyndaqel N=64	P-value	Vyndaqel % change relative to Placebo
NIS-LL change from BL	5.8 (0.96)	2.8 (0.95)	0.027	-52%

LSMean (SE)				
Large Fibre change from BL *LSMean (SE)*	3.2 (0.63)	1.5 (0.62)	0.066	-53%
Small Fibre change from BL *LSMean (SE)*	1.6 (0.32)	0.3 (0.31)	0.005	-81%
mBMI change from BL *LSMean (SE)*	-33.8 (11.8)	39.3 (11.5)	<0.0001	NA
mBMI was derived as the product of serum albumin and Body Mass Index. Based on repeated measures analysis of variance with change from baseline as the dependent variable, an unstructured covariance matrix, treatment, month and treatment-by-month as fixed effects, and subject as a random effect in the model. NA=not applicable.				

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

Although data are limited, (one open-label study in 21 patients), taking into account the mechanism of action of tafamidis and the results on TTR stabilisation, tafamidis meglumine is expected to be beneficial in patients with stage 1 ATTR-PN due to mutations other than V30M.

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

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

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

This medicinal product has been authorised under ‘exceptional circumstances’.
This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product..

Therefore any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

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

Biotransformation and elimination

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

Dose and time linearity

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

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

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

Special populations

Hepatic impairment

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

Renal impairment

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

Elderly

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

Pharmacokinetic/pharmacodynamic relationships

In vitro data indicated that tafamidis does not significantly inhibit cytochrome P450 enzymes CYP1A2, CYP3A4, CYP3A5, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Tafamidis is

not expected to cause clinically relevant drug interaction due to induction of CYP1A2, CYP2B6 or CYP3A4.

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

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

5.3 Preclinical safety data

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

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

In the rat pre- and post-natal development study with tafamidis, decreased pup survival and reduced pup weights were noted following maternal dose administration during pregnancy and lactation at doses of 15 and 30 mg/kg/day. Decreased pup weights in males were associated with delayed sexual maturation (preputial separation) at 15 mg/kg/day. Impaired performance in a water-maze test for learning and memory was observed at 15 mg/kg/day. The NOAEL for viability and growth in the F1 generation offspring following maternal dose administration during pregnancy and lactation with tafamidis was 5 mg/kg/day (human equivalent dose =0.8 mg/kg/day), a dose approximately 4.6-times the clinical dose of 20 mg tafamidis meglumine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell
Gelatine Clear
Gelatine (195 AH 8)
Sorbitol Special-Glycerin Blend
Purified Water
Iron Oxide, Yellow
Titanium Dioxide
Purified Water

Capsule contents

Polyethylene Glycol 400
Polysorbate 80
Sorbitan Monooleate

Printing ink Purple Opacode® (WB)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

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

Pack size: 30 soft capsules

6.6 Special precautions for disposal

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

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