ANNEX I

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

1 NAME OF THE MEDICINAL PRODUCT

Vyndaqel 20 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients: Each soft capsule contains 77.2 mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule.

Off-white to light yellow, opaque, oblong (approximately 21.5 mm) capsule imprinted with “FX 6A” in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

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 by and remain under the supervision of a physician knowledgeable in the management of patients with transthyretin amyloid polyneuropathy.

Posology

The recommended dose of Vyndaqel is 20 mg orally once daily.

Vyndaqel should be added to the standard of care for the treatment of the transthyretin familial amyloid polyneuropathy (TTR-FAP) patient. 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 Vyndaqel post-liver transplantation, Vyndaqel should be discontinued in patients who undergo liver transplantation.

Special populations

Paediatric population

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

Elderly

Data in the elderly patients are very limited.
No dosage adjustment is required for elderly patients (≥ 65 years).
Patient with hepatic and renal impairment

No dosage adjustment is required for patients with renal or mild and moderate hepatic impairment. Tafamidis has not been studied in patients with severe hepatic impairment and caution is recommended (see section 5.2).

Method of administration

Oral use.

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

If vomiting occurs shortly after dosing, and 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 Vyndaqel dosing the next day as usual.

4.3 Contraindications

Hypersensitivity to the active substance(s) 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 Vyndaqel and continue to use appropriate contraception for 1-month after stopping treatment with Vyndaqel (see section 4.6).

Vyndaqel contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

In vitro studies with tafamidis suggest that it is unlikely tafamidis will cause drug interactions at clinically relevant concentrations with substrates of UDP glucuronosyltransferase (UGT), P-gp transporters, or organic anion-transporting polypeptide transporters (OATP1B1 and 1B3).

However, 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, rosvuastatin, imatinib). 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).

No interaction studies have been performed evaluating the effect of other medicinal products on tafamidis.
4.6 Fertility, pregnancy and lactation

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

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

Breast-feeding
Available pharmacodynamic/toxicological data in animals have shown excretion of tafamidis in milk. A risk to the newborns/infants cannot be excluded. Vyndaqel 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

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

4.8 Undesirable effects

TTR amyloid polyneuropathy is a rare disorder. The overall clinical data reflect exposure of 127 TTR amyloid polyneuropathy patients to 20 mg of tafamidis administered daily for an average of 538 days (ranging from 15 to 994 days). The adverse reactions were generally mild or moderate in severity.

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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>Vaginal infection</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Upper abdominal pain</td>
</tr>
</tbody>
</table>

Reporting of suspected adverse reactions

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

4.9 Overdose

No cases of acute overdose have been reported. In clinical trials of healthy volunteers, the highest dose of tafamidis given was 480 mg in a single dose and 60 mg once daily for two weeks. The reported treatment-related adverse events were mild to moderate and included: headache, somnolence, myalgia, insomnia, hordeolum, photosensitivity reaction, and presyncope.
5 PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code N07XX08

Mechanism of action

Tafamidis is a novel specific stabilizer of transthyretin.

Pharmacodynamic effects

TTR amyloid polyneuropathy is a multi-faceted, progressive, axonal degenerative neuropathy characterized by sensory, motor and autonomic impairment. The dissociation of the transthyretin tetramer to monomers is the rate limiting step in the pathogenesis of TTR amyloid polyneuropathy, also known as TTR familial amyloid polyneuropathy (TTR-FAP). 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 non-cooperatively to the two thyroxine binding sites on the native tetrameric form of transthyretin preventing dissociation into monomers. The inhibition of transthyretin tetramer dissociation forms the rationale for the use of tafamidis to slow disease progression.

Clinical efficacy and safety

The pivotal study of Vyndaqel was an 18-month, multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of once-daily 20 mg tafamidis in 128 patients with TTR amyloid polyneuropathy with the V30M mutation and primarily stage 1 disease (do 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 fiber (nerve conduction, vibration threshold and heart rate response to deep breathing - HRDB) and small nerve fiber 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 for an additional 12 months.

Following 18 months of treatment, more Vyndaqel-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)

#### Pre-specified ITT Analysis

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vyndaqel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=61</td>
<td>N=64</td>
<td></td>
</tr>
<tr>
<td>NIS-LL Responders (% Patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference (Vyndaqel minus Placebo)</td>
<td>29.5%</td>
<td>45.3%</td>
</tr>
<tr>
<td>95% CI of Difference (p-value)</td>
<td>-0.9%, 32.5% (0.068)</td>
<td>15.8%</td>
</tr>
<tr>
<td>TQOL Change from Baseline LSMean (SE)</td>
<td>7.2 (2.36)</td>
<td>2.0 (2.31)</td>
</tr>
<tr>
<td>Difference in LSMeans (SE)</td>
<td>-5.2 (3.31)</td>
<td>-11.8, 1.3 (0.116)</td>
</tr>
<tr>
<td>95% CI of Difference (p-value)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Pre-specified Efficacy Evaluable Analysis

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vyndaqel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=42</td>
<td>N=45</td>
<td></td>
</tr>
<tr>
<td>NIS-LL Responders (% Patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference (Vyndaqel minus Placebo)</td>
<td>38.1%</td>
<td>60.0%</td>
</tr>
<tr>
<td>95% CI of Difference (p-value)</td>
<td>1.4%, 42.4% (0.041)</td>
<td>21.9%</td>
</tr>
<tr>
<td>TQOL Change from Baseline LSMean (SE)</td>
<td>8.9 (3.08)</td>
<td>0.1 (2.98)</td>
</tr>
<tr>
<td>Difference in LSMeans (SE)</td>
<td>-8.8 (4.32)</td>
<td>-17.4, -0.2 (0.045)</td>
</tr>
<tr>
<td>95% CI of Difference (p-value)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 Vyndaqel 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)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vyndaqel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=61</td>
<td>N=64</td>
<td>P-value</td>
</tr>
<tr>
<td>NIS-LL change from BL</td>
<td>5.8 (0.96)</td>
<td>2.8 (0.95)</td>
</tr>
<tr>
<td>LSMean (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large Fiber change from BL</td>
<td>3.2 (0.63)</td>
<td>1.5 (0.62)</td>
</tr>
<tr>
<td>LSMean (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Fiber change from BL</td>
<td>1.6 (0.32)</td>
<td>0.3 (0.31)</td>
</tr>
<tr>
<td>LSMean (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mBMI change from BL</td>
<td>-33.8 (11.8)</td>
<td>39.3 (11.5)</td>
</tr>
<tr>
<td>LSMean (SE)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mBMI was derived as the product of serum albumin and Body Mass Index.

NA=Not applicable

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.

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, Vyndaqel is expected to be beneficial in patients with stage 1 TTR amyloid polyneuropathy due to mutations other than V30M.
The effects of tafamidis on cardiac disease progression have not yet been adequately characterised. A supra-therapeutic, single, 400 mg oral dose of tafamidis solution in healthy volunteers demonstrated no prolongation of the QTc interval.

The European Medicines Agency has waived the obligation to submit the results of studies with Vyndaqel in all subsets of paediatric population in neuropathic heredofamilial amyloid polyneuropathy (see section 4.2 for information on paediatric use).

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

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

After oral administration of the soft capsule, the maximum plasma concentration (C_max) is achieved at a median time (t_max) of 1.75 hours after dosing in the fasted state. Concomitant administration of food decreased 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 (99.9%) in plasma. The apparent steady state volume of distribution is 25.7 liters.

Biotransformation

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. Following daily administration of a 20 mg dose of tafamidis for 14 days in healthy subjects, mean steady-state half-life was 59 h and mean total clearance was 0.42 l/h.

Dose and time linearity

Results from once-daily dosing with tafamidis 15, 30, or 60 mg for 14 days demonstrated dose-dependent increases in C_max and AUC between doses of 15 mg and 30 mg and less than dose proportional between 30 and 60 mg, indicating saturation of absorption process beyond 30 mg.

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

Results of once-daily dosing with tafamidis 20 mg for 14 days demonstrated that steady-state was achieved by Day 14. C_max(ss) and C_min(ss) was 2.7 and 1.6 µg/ml, respectively.

Special populations

Hepatic impairment

Pharmacokinetic data indicated decreased systemic exposure (approximately 40%) and increased total clearance (0.52 l/h vs. 0.31 l/h) of tafamidis 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 stabilization 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 patients with renal impairment, but a dosage adjustment in patients with renal impairment is considered not necessary.

*Elderly*

Based on population PK results, subjects older than 60 years old had an average 19% lower estimate of clearance at steady-state compared to subjects less than 60 years old. However, the difference in clearance would not be clinically significant and would not result in clinically relevant different steady-state levels compared to younger subjects.

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity.

In repeated dose toxicity studies the liver appeared as a target organ for toxicity in the different species tested. Liver effects were seen at doses above (>3) human exposure and have generally been shown to be reversible.

There was no evidence of adverse reactions of tafamidis on fertility, reproductive performance or mating behaviour in the rat at any dose level.

In a developmental toxicity study in rabbits, a slight increase in skeletal malformations and variations, abortions in few females, and reduction in foetal weights were observed at an AUC_{0-24} ratio of 3.2-fold, based on the human AUC at steady state.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell
- Gelatin
- Glycerin
- Sorbitol liquid (E420)
- Titanium dioxide (E171)
- Purified water

Capsule contents
- Macrogol
- Sorbitan monooleate
- Polysorbate 80
Printing ink (Opacode black)
Shellac glaze 45% (20% esterified) in ethanol
Isopropyl alcohol
Iron oxide black (E172)
Propylene glycol
Ammonium hydroxide 28%

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months

6.4 Special precautions for storage
Do not store above 25°C. Store in the original container in order to protect from light.

6.5 Nature and contents of container
Two polyvinyl chloride/aluminum blisters each containing 15 soft capsules are contained in a wallet.

Pack sizes: 30 or 90 soft capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Pfizer Limited
Ramsgate Road
Sandwich, Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
EU/1/11/717/001
EU/1/11/717/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 16 November 2011

10 DATE OF REVISION OF THE TEXT
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE
B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION
D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES
A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Penn Pharmaceutical Services Limited
Units 23-24, Tafarnaubach Industrial Estate
Tafarnaubach
Tredegar
Gwent
NP22 3AA
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

- Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- Additional Risk Minimisation Measures

The Physician Information Leaflet should contain the following key messages:
- The need to counsel patients on important risks associated with Vyndaqel therapy and appropriate precautions when using the medicine, particularly the avoidance of pregnancy and the need for effective contraception.
• That patients should be advised to contact their doctor about adverse events and that physicians/pharmacists should report suspected adverse reactions to Vyndaqel since there is limited knowledge about the clinical safety due to the rare nature of transthyretin amyloidosis.

• That physicians are encouraged to enter patients in the Transthyretin Amyloidosis Outcome Survey (THAOS) and provided with details how to enroll patients into this international disease registry

• The existence and scope of the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) program and the details how to report pregnancies in women who are being treated with Vyndaqel.

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

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

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within the planned post-authorisation sub-study of the THAOS registry the MAH shall evaluate in non-V30M patients the effects of Vyndaqel on disease progression and its long term safety as detailed in a CHMP agreed protocol, and shall provide yearly updates on the collected data within the annual re-assessment.</td>
<td>Annual Reassessment</td>
</tr>
</tbody>
</table>


ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON</th>
</tr>
</thead>
</table>

1. NAME OF MEDICINAL PRODUCT

Vyndaqel 20 mg soft capsules
tafamidis

2. STATEMENT OF ACTIVE SUBSTANCES

Each soft capsule contains 20 mg tafamidis meglumine equivalent to 12.2 mg tafamidis base

3. LIST OF EXCIPIENTS

The capsule contains sorbitol (E420). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 soft capsules
90 soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original container in order to protect from light.
**10** SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

**11** NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

**12** MARKETING AUTHORISATION NUMBER(S)

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

**13** BATCH NUMBER

Lot

**14** GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

**15** INSTRUCTIONS ON USE

Lift here

**16** INFORMATION IN BRAILLE

Vyndaqel
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat sealed blister card of 30 x 20 mg tafamidis soft capsules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1</th>
<th>NAME OF MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Vyndaqel 20 mg soft capsules tafamidis</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>2</th>
<th>NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tr>
<td>Pfizer Limited (as MA Holder logo)</td>
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<table>
<thead>
<tr>
<th>5</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>To remove capsule push through from this side</td>
<td></td>
</tr>
<tr>
<td>Fold and reclose after removing capsule</td>
<td></td>
</tr>
<tr>
<td>Pull here</td>
<td></td>
</tr>
<tr>
<td>Day 1 to Day 30</td>
<td></td>
</tr>
</tbody>
</table>
B. PACKAGE LEAFLET
Package leaflet: Information for the user

Vyndaqel 20 mg soft capsules
Tafamidis

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

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

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

What is in this leaflet

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

1. What Vyndaqel is and what it is used for

Vyndaqel contains the active substance tafamidis.

Vyndaqel is a medicine which treats a disease called Transthyretin (TTR) amyloid polyneuropathy, also known as TTR familial amyloid polyneuropathy (TTR-FAP). TTR amyloid polyneuropathy is caused by a protein called TTR that does not work properly. TTR is an important protein that carries other substances, such as hormones, through the body.

In patients with this disease, TTR breaks up and may form fibres called amyloid. Amyloid can build up around your nerves and in other places in your body, preventing them from working normally. Eventually, the amyloid causes the symptoms of this disease.

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

2. What you need to know before you take Vyndaqel

Do not take Vyndaqel

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Vyndaqel.
• Women that can become pregnant should use birth control while taking Vyndaqel and should continue using birth control for one month after stopping treatment with Vyndaqel.

**Children and adolescents**

Children and adolescents do not have the symptoms of TTR amyloid polyneuropathy. Vyndaqel is therefore not used for children and adolescents.

**Other medicines and Vyndaqel**

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

**Pregnancy and breast-feeding and fertility**

- You should not take Vyndaqel if you are pregnant or breast-feeding. Talk to your doctor or pharmacist if you are pregnant, think you may be pregnant, or plan to become pregnant.
- If you are able to become pregnant, you should use birth control during treatment and for one month after stopping treatment.

**Driving and using machines**

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

**Vyndaqel contains sorbitol**

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

**3. How to take Vyndaqel**

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

The recommended dose is one capsule (20 mg) of Vyndaqel once a day, taken with or without food.

The capsule should be swallowed whole, and not crushed or cut.

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

**If you take more Vyndaqel than you should**

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

**If you forget to take Vyndaqel**

Take your capsules as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.
If you stop taking Vyndaqel

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

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

4. Possible side effects

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

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

Reporting of side effects

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

5. How to store Vyndaqel

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

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

Do not store above 25°C. Store in the original package in order to protect from light.

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

6. Contents of the pack and other information

What Vyndaqel contains

- The active substance is tafamidis. Each capsule contains 20 mg tafamidis meglumine equivalent to 12.2 mg tafamidis base.
- The other ingredients are: gelatin, glycerin, sorbitol liquid, titanium dioxide, purified water, macrogol, sorbitan monooleate, polysorbate 80, shellac glaze, isopropyl alcohol, iron oxide black, propylene glycol and ammonium hydroxide.

What Vyndaqel looks like and contents of the pack

Vyndaqel soft capsules are off-white to light yellow, opaque, oblong (approximately 21.5 mm) imprinted with “FX 6A” in black ink. They are supplied on a blister card of 15 soft capsules. There are
2 blister cards in each wallet. A pack of 30 or 90 soft capsules is provided. Not all pack sizes may be marketed.

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

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

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

Other sources of information

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

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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