PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VYNDAQEL (TAFAMIDIS MEGLUMINE / TAFAMIDIS)

Marketing Authorization Numbers 67083 and 67518

Capsule, soft, 20 mg tafamidis meglumine; Capsule, soft, 61 mg tafamidis

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LIST OF ABBREVIATIONS

ATTR	Transthyretin amyloid
CM	Cardiomyopathy
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
EU	European Union
HCP	Healthcare Professional
NYHA	New York Heart Association
PN	Peripheral Neuropathy
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TBG	Thyroxine Binding Globulin
TESPO	Tafamidis Enhanced Surveillance Pregnancy Outcomes
TSH	thyroid-stimulating hormone
TTR	Transthyretin

OVERVIEW

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary for Vyndaqel is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss marketing authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Vyndaqel in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Pfizer AG is fully responsible for the accuracy and correctness of the content of the published RMP summary of Vyndaqel.

SUMMARY OF RISK MANAGEMENT PLAN FOR VYNDAQEL 20 MG (TAFAMIDIS MEGLUMINE) AND VYNDAQEL 61 MG (TAFAMIDIS)

This RMP details important risks of Vyndaqel, how these risks can be minimised, and how more information will be obtained about Vyndaqel's risks and uncertainties (missing information).

Vyndaqel's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vyndaqel should be used.

This summary of the RMP for Vyndaqel should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vyndaqel's RMP.

I. The Medicine and What It Is Used For

Vyndaqel is authorised for the treatment of transthyretin amyloidosis (ATTR) in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment and is proposed for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (see SmPC for the full indication). It contains tafamidis meglumine or tafamidis free acid as the active substance and it is given by oral route of administration.

Further information about the evaluation of Vyndaqel’s benefits can be found in Vyndaqel’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:
https://www.ema.europa.eu/documents/overview/vyndaqel-epar-summary-public_en.pdf

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Vyndaqel, together with measures to minimise such risks and the proposed studies for learning more about Vyndaqel's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Vyndaqel is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Vyndaqel are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vyndaqel. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1. List of important risks and missing information

Important identified risks	None
Important potential risks	Hepatotoxicity Reproductive and developmental toxicity and lactation Changes in thyroid function, particularly in pregnant women
Missing information	Patients with NYHA Class IV (ATTR-CM indication) Patients with severe hepatic impairment Safety and efficacy in patients with ATTR-PN mutations other than Val30Met

II.B. Summary of Important Risks

Table 2. Important Potential Risks

Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Data are from nonclinical toxicity studies in rodents. Tafamidis-associated hepatic alterations in nonclinical studies were observed at exposures approximately ≥0.7-times the human exposure at a dose of 61 mg tafamidis and 2.5-times the human exposure at a dose of 20 mg tafamidis meglumine. The observed liver findings were largely consistent with induction of adaptive responses to xenobiotic exposure in rodents and/or exacerbation of normal aging changes and, consequently, are not relevant to human safety. The absence of findings in clinical databases for both ATTR-PN and ATTR-CM studies support the lack of relevance to human safety.
Risk factors and risk groups	All patients receiving tafamidis.
Risk Minimisation Measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None.
Additional Pharmacovigilance Activities	None.

Table 2. Important Potential Risks

Important Potential Risk: Reproductive and developmental toxicity and lactation	
Evidence for linking the risk to the medicine	Data are from nonclinical toxicity studies. In an embryo-fetal developmental toxicity study in rabbits, a slight increase in skeletal malformations and variations, abortions in few females, reduced embryo-fetal survival, and reduction in fetal weights were observed. Postnatal mortality, growth retardation, and impaired learning and memory were observed in offspring of pregnant rats administered tafamidis meglumine during gestation and lactation. Tafamidis is secreted in the milk of lactating rats. The relevance to humans is unknown.
Risk factors and risk groups	All pregnant and lactating women receiving tafamidis.
Risk Minimisation Measures	Routine risk minimisation measures SmPC Section 4.4 Special warnings and precautions for use SmPC section 4.6 Fertility, pregnancy and lactation. Additional risk minimisation measures: HCP Guide
Additional Pharmacovigilance Activities	TESPO programme.
Important Potential Risk: Changes in thyroid function, particularly in pregnant women	
Evidence for linking the risk to the medicine	Data suggest that any displacement of thyroxine due to tafamidis binding would be minimal and the risk that it might impact thyroid hormone homeostasis is unlikely. This assessment is supported by the observation that perturbations in any of the binding globulins are not associated with abnormalities in thyroid hormone homeostasis but rather maintenance of the euthyroid state is observed. In fact, in the presence of normal levels of TBG, wide fluctuations in TTR concentration, or its removal from serum by specific antibodies has little influence on the concentration of free T4. In addition, mice lacking TTR maintain an euthyroid status despite a 50% reduction in total circulating T4 levels. Due to the theoretical risk of thyroid function abnormalities related to displacement of thyroxine from the thyroxine binding site on the transthyretin tetramer, a comprehensive assessment of thyroid function was performed throughout the tafamidis ATTR-PN clinical programme. This included assessment of TSH and total and free thyroxine in healthy volunteers and in all patient studies. Monitoring of thyroid hormone (including TSH and total and free thyroxine) in the tafamidis clinical trials did not demonstrate perturbations of thyroid hormone status. In placebo controlled clinical studies in ATTR-PN, changes from baseline to Month 18 in thyroid function were similar between the treatment groups. No significant changes from baseline were observed, and mean change for tafamidis was similar to that for placebo at all time points. Given that the mean changes were similar between the treatment groups, and the mean values remained within the normal range, there appears to be only a theoretical risk of tafamidis effect on thyroid function. In Study B3461028 (ATTR-CM), a small decrease from baseline in mean total thyroxine values was observed in both the tafamidis 20 mg and tafamidis 80 mg groups (with greater decrease in tafamidis 80 mg) across visits; however, there were no clinically meaningful shifts in the free T4 or TSH values noted. This is also corroborated by the absence of an observed safety signal in thyroid dysfunction adverse events in the tafamidis-treated patients. This observation in total thyroxine values may likely be the result of reduced thyroxine binding to or displacement from TTR due to the high binding affinity tafamidis has to the TTR thyroxine receptor.
Risk factors and risk groups	All patients receiving tafamidis.
Risk Minimisation Measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use

Table 2. Important Potential Risks

	SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction Additional risk minimisation measures: None.
Additional Pharmacovigilance Activities	None.

Table 3. Missing Information

Missing information: Patients with NYHA Class IV (ATTR-CM indication)	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections: Section 4.2 Posology and method of administration Additional risk minimisation measures: HCP Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Missing information: Patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections: Section 4.2 Posology and method of administration Section 5.2: Pharmacokinetic properties Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Missing information: Safety and efficacy in patients with ATTR-PN mutations other than Val30Met	
Risk minimisation measures	Routine risk minimisation measures: Vyndaqel 20 mg SmPC Sections: 5.1, Pharmacodynamic properties Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Yearly updates on any new information concerning the effects of tafamidis on disease progression and its long-term safety in non-Val30Met patients.

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

- Category 1 (imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation): None

- Category 2 (imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances): Yearly updates on any new

information concerning the effects of tafamidis on disease progression and its long-term safety in non-Val30Met patients.

II.C.2. Other Studies in Post-Authorisation Development Plan

Category 3 (required additional pharmacovigilance activities): 1 ongoing

Study short name: Tafamidis enhanced surveillance pregnancy outcomes (TESPO)

Purpose of the study: The TESPO program is intended to improve data collection on pregnancy and pregnancy outcomes in this limited population of patients who receive tafamidis during or within a month prior to pregnancy.