

Pfizer's Vyndaqel® (tafamidis) First Therapy Approved in the European Union for the Rare and Fatal Neurodegenerative Disease Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP)

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Approval Represents a Major Advance, as Vyndaqel is the First and Only Medication Currently Approved to Delay Peripheral Neurologic Impairment in Stage 1 TTR-FAP Patients

"A diagnosis of TTR-FAP, usually made in patients during their mid-life years, impacts both the physical and emotional well-being of patients and caregivers and significantly limits daily activities,"

[\(BUSINESS WIRE\)](#)--Pfizer announced today that the European Commission has approved Vyndaqel® (tafamidis) for the treatment of Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP) in adult patients with stage 1 symptomatic polyneuropathy. TTR-FAP is a rare, progressive and fatal neurodegenerative disease that affects approximately 8,000 patients worldwide. ^{1,2,3}

"A diagnosis of TTR-FAP, usually made in patients during their mid-life years, impacts both the physical and emotional well-being of patients and caregivers and significantly limits daily activities," said Dr. Teresa Coelho, Hospital Santo Antonio in Porto, Portugal, who participated in the clinical trials of Vyndaqel. "Until now, there were no approved medications to treat this degenerative and fatal disease. Vyndaqel offers new hope to patients who are diagnosed with TTR-FAP."

Mutations of the transthyretin (TTR) gene can result in the production of unstable TTR proteins which can accumulate as amyloid fibrils. Amyloid fibrils can deposit in a variety of organs including the nerves, heart and kidneys, interfering with normal function.^{3,4} Vyndaqel is a novel specific transthyretin stabilizer designed to prevent the formation of these misfolded proteins and the subsequent amyloid deposits that induce neurodegeneration and decline of neurologic function.³ In the pivotal trial (Fx-005), transthyretin stabilization (as demonstrated by an *in vitro* assay) was observed in 98 percent of patients on Vyndaqel, and in no patients on placebo, at 18 months.⁵

"Today marks a real breakthrough for patients in the EU living with TTR-FAP," said Yvonne Greenstreet, senior vice president and head of Medicines Development Group for Pfizer's Specialty Care Business Unit. "This community urgently needs an effective therapy, and we are proud to be able to provide the first and only approved medication for patients with this rare and debilitating genetic disease. Pfizer is focused on meeting the needs of patients suffering from rare diseases and this approval is an important step forward in our commitment to providing treatment options for patients."

The approval is based on results from a pivotal clinical trial (Fx-005) and an open-label, 12-month extension study (Fx-006), which evaluated the long-term safety and efficacy of Vyndaqel in patients with TTR-FAP. Across these clinical studies, Vyndaqel showed efficacy in delaying peripheral neurologic impairment. Additional data from these studies showed 51 to 81 percent less deterioration in neurologic function, large fiber function (measure of motor strength) and small fiber function (measure of sensation) compared with patients treated with placebo. Vyndaqel resulted in improved nutritional status (modified body mass index or mBMI); decline in mBMI was shown to correlate with disease progression in the pivotal 18-month study.⁵

The adverse drug reactions reported in the pivotal study of Vyndaqel were diarrhea, upper abdominal pain, urinary tract infection and vaginal infection.⁵

Pfizer is working closely with the relevant national health authorities across the EU to launch the new treatment and anticipates that health care professionals will be able to prescribe the treatment in European markets by early 2012.

About Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP)

Mutations of the transthyretin (TTR) gene can result in the production of unstable TTR proteins which can accumulate as amyloid fibrils. Amyloid fibrils can deposit in a variety of organs including the nerves, heart and kidneys, interfering with normal function.^{3,4} Patients with TTR-FAP experience significantly diminished quality of life due to symptoms including polyneuropathy characterized by sensory loss, pain and weakness in the lower limbs; as well as severe impairment of the autonomic nervous system commonly manifesting as erectile dysfunction, alternating diarrhea and constipation, unintentional weight loss, orthostatic hypotension, urinary incontinence, urinary retention and delayed gastric emptying.^{3,4,6,7} As the disease progresses, patients often lose the ability to walk, needing wheelchair assistance, and eventually become bedridden and unable to care for themselves.^{7,8,9} TTR-FAP typically occurs during active adult years with onset as early as the 30s, followed by disease progression that reaches the terminal stage in approximately 10 years on average.^{4,7,10}

About Vyndaqel® (tafamidis)

Vyndaqel is a novel specific TTR stabilizer indicated in the EU for the treatment of TTR amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.⁵

Further details and product information will be available in the European Public Assessment Report on the website of the European Medicines Agency at www.emea.europa.eu.

About study Fx-005 (Pivotal Phase II/III Study)

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 Vyndaqel in 128 patients with TTR amyloid polyneuropathy with the V30M mutation and primarily stage 1 disease. The primary outcome measures were the Neuropathy Impairment Score - 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). Other outcome measures included composite scores of large nerve fiber and small nerve fiber function and nutritional assessments utilizing the modified body mass index (mBMI).⁵

While the pivotal study missed its co-primary endpoints, it did meet statistical significance in a predefined secondary analysis, which was designed to adjust for the impact of patient attrition due to liver transplantation.⁶ Following 18 months of treatment, more Vyndaqel-treated patients were NIS-LL responders (showed less deterioration in neurologic function as measured by the NIS-LL), and the secondary end points demonstrated that Vyndaqel treatment resulted in less deterioration of neurologic function and improved nutritional status

(mBMI) compared with placebo. Transthyretin stabilization (as demonstrated by an *in vitro* assay) was observed in 98 percent of patients on Vyndaqel, and in no patients on placebo, at 18 months.⁵

The adverse drug reactions reported in the pivotal study of Vyndaqel were diarrhea, upper abdominal pain, urinary tract infection and vaginal infection.⁵

About study Fx-006 (Open-Label Extension Study)

In a 12-month, open-label, single-treatment arm extension of the 18-month, double-blind, placebo-controlled trial, investigators evaluated the longer-term effect of Vyndaqel as a treatment for TTR-FAP. In this study, all patients were treated with Vyndaqel. The study evaluated groups identified by the treatment sequence patients received in the respective trials (Vyndaqel-Vyndaqel or placebo-Vyndaqel).⁵

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 randomized and treated with Vyndaqel in the previous double-blind 18-month period. No new safety issues were identified in this open-label extension study.⁵

About Pfizer's Specialty Care Business

Pfizer's Specialty Care Business Unit is the world's largest specialty pharmaceuticals business, with a commitment to the eradication, remission, and relief of serious diseases. Pfizer's Specialty Care Business Unit brings together the best scientific minds to challenge the most feared diseases of our time, and we seek solutions to prevent and relieve suffering of patients with serious diseases, regardless of prevalence. Pfizer is an established global leader in rare diseases, offering marketed products treating 17 orphan indications in the U.S. to address the unique needs of small patient populations affected by uncommon and often life-threatening conditions. We are on the front lines of discovering innovative medicines and delivering hope through continued focus on research, development and commercialization of orphan medicines.

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DISCLOSURE NOTICE: The information contained in this release is as of November 17, 2011. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information that involves substantial risks and uncertainties about Vyndaqel® (tafamidis), including its potential benefits and the expected timing of availability in European markets. Such risks and uncertainties include, among other things, when the relevant national health authorities across the EU will authorize the launch of Vyndaqel in the respective markets.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2010 and in its reports on Form 10-Q and Form 8-K.

¹ Dattilo PB. Familial (ATTR) amyloidosis misdiagnosed as primary (AL) variant: a case report. *Cases J.* 2009;2:9295-9298.

² Ando Y, Nakamura M, Araki S. Transthyretin-related familial amyloidotic polyneuropathy. *Arch Neurol.* 2005;62:1057-1062.

³ Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. *Muscle Nerve.* 2007;36:411-423.

⁴ Hou X, Aguilar M-I, Small DH. Transthyretin and familial amyloidotic polyneuropathy: recent progress in understanding the molecular mechanism of neurodegeneration. *FEBS J.* 2007;274:1637-1650.

⁵ Data on file Pfizer Inc, New York, NY.

⁶ Sekijima Y, Yoshida K, Tokuda T, Ikeda S. Familial transthyretin amyloidosis. In: Pagon RA, Bird TD, Dolan CR, Stephens K, eds. *GeneReviews* [Internet]. Seattle WA: University of Washington, Seattle; 1993-2009. <http://www.ncbi.nlm.nih.gov/books/NBK1194/>. Accessed January 31, 2011.

⁷ Jonsèn E, Athlin E, Suhr O. Familial amyloidotic patients' experience of the disease and of liver transplantation. *J Adv Nurs.* 1998;27:52-58.

⁸ Coutinho P, da Silva AM, Lima JL, Barbosa AR. Forty years of experience with type 1 amyloid neuropathy: review of 483 cases. In: Glenner GG, e Costa PP, de Freitas AF, eds. *Amyloid and Amyloidosis.* Amsterdam: Excerpta Medica; 1980:88-98.

⁹ Suhr OB, Svendsen IH, Andersson R, et al. Hereditary transthyretin amyloidosis from a Scandinavian perspective. *J Intern Med.* 2003;254:225-235.

¹⁰ Plante-Bordeneuve V, Ferreira A, Lalu T, et al. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). *Neurology.* 2007;69:693-698.

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Vyndaqel(R) (tafamidis) is the first and only medication approved for the treatment of Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP) in adult patients with stage 1 symptomatic polyneuropathy. (Photo: Business Wire)

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Hear Dr. Teresa Coelho, Hospital Santo Antonio in Porto, Portugal, discuss the devastating impact of TTR-FAP on patients.

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Learn about how the TTR-FAP mechanism of disease leads to neurodegeneration and decline of neurologic function.

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