Recommendation No. 141/2021
of 23 December 2021
of the President of the Agency for Health Technology Assessment and Tariff System
on the reimbursement of Vyndaqel, Tafamidis, soft capsules, 61 mg, 30 capsules (1 × 30), GTIN code: 05415062359426 for use under the drug programme "Treatment of transthyretin amyloid cardiomyopathy with tafamidis in adults (ICD-10 E85)"

The President of the Agency does not recommend the reimbursement of Vyndaqel, Tafamidis, soft capsules, 61 mg, 30 capsules, GTIN code: 05415062359426 for use under the drug programme "Treatment of transthyretin amyloid cardiomyopathy with tafamidis in adults (ICD-10 E85)" as proposed in the application.

Grounds for the recommendation

The main reason against financing Vyndaqel as proposed in the application stems from the results of the economic analysis, according to which the estimated value of ICUR [information protected as a trade secret] the cost-effectiveness threshold -the estimated ICUR was [information protected as a trade secret]. According to the probabilistic analysis, the probability of achieving cost-effectiveness [information protected as a trade secret].

The results of the clinical analysis were taken into account, which included a randomised clinical trial (ATTR-ACT), in which the intervention was tafamidis meglumine, a tafamidis bioequivalent. The RCT population consisted of adults (approx. 75 years old on average) with ATTRwt or ATTRm cardiomyopathy and confirmed amyloid deposits following the analysis of biopsy samples. The use of tafamidis meglumine 80 mg was associated with statistically significant reductions in total mortality (HR = 0.690) and in the frequency of hospitalisation due to cardiovascular issues (RR = 0.70).

The reimbursement of Vyndaqel will result in a significant increase in expenses of the entity obliged to finance the interventions from public funds. Incremental expenses, when the RSS is considered, will be [information protected as a trade secret] in the 1st year of the reimbursement and [information protected as a trade secret] in the 2nd year of the reimbursement.

The consideration process also included reimbursement recommendations with different opinions. Negative recommendations indicate the lack of cost-effectiveness, while the condition included in the positive CADTH recommendation is to reduce the price.

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of financing the following medicinal products from public funds:

- Vyndaqel, Tafamidis, soft capsules, 61 mg, 30 capsules, GTIN code: 05415062359426, proposed net sales price [information protected as a trade secret].

Proposed payment and dispensing category: patient payment - free of charge, product available under the drug programme "Treatment of transthyretin amyloid cardiomyopathy with tafamidis in adults (ICD-10 E85)", financed under a new limit group. [information protected as a trade secret]

Health problem

Cardiomyopathies are a group of diseases of various aetiology that affect heart muscles and lead to cardiac dysfunction. Amyloidosis is a systemic disease in which organ damage results from the accumulation of extracellular protein deposits in the form of fibrils with a β-harmonic structure - i.e. amyloid composed of circulating protein precursors. Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by the accumulation of amyloid fibres in the extracellular matrix of the heart. This results in a gradual deterioration of the diastolic function, and in more advanced stages - of the systolic function, which leads to the development of hypertrophic cardiomyopathy or restrictive cardiomyopathy. There are two forms of ATTR: acquired wild-type ATTR (ATTRwt), referred to as senile amyloidosis; and hereditary ATTR (mutant ATTR - ATTRm, hereditary ATTR - ATTRh, variant ATTR - ATTRv).

Patients with ATTR-CM often have shortness of breath, fatigue and swelling of the lower limbs. These symptoms are non-specific and are often misdiagnosed as non-amyloid heart failure with preserved ejection fraction (HFpEF). Median survival from diagnosis is 3.6-4.8 years for ATTRwt CM, 2.6 years for ATTRv-CM due to the identified Val122Ile mutation and 5.8 years for ATTRv-CM due to other mutations.

Wild-type transthyretin amyloidosis most often affects older men with heart failure, sometimes co-exists with carpal tunnel syndrome and lumbar spinal stenosis. The autosomal dominant hereditary form of ATTRh develops through a mutation in the TTR gene. Patients with ATTRh develop symptoms of cardiomyopathy, depending on the type of mutation, at the age of 30-50. Median survival from diagnosis to death is 2-6 years. Reports currently published in Poland are limited to a few cases, with epidemiological data being unknown.

In Polish actual clinical practice, a total of 111 treated patients were identified in the period from January 2014 to December 2020. In 2020, the number of newly diagnosed patients was 21, while there were 57 living patients already diagnosed in previous years.
The average age of patients in the analysed population was 61.6 ± 10.94 years. Patients in the target group of the application are a highly heterogeneous group, with multiple diseases. Comorbidities include stomach ulcers, gout, dyslipidemia (nutrition-related diseases), infections and infectious diseases, allergies but also cancers or thyroid diseases.

Alternative health technology

According to available guidelines, the basis of treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) is symptomatic treatment of heart failure. There is no alternative health technology understood as active treatment.

The applicant indicated the use of a placebo as a comparator, i.e. to compare the efficacy of tafamidis with the natural history of the disease. The selection of the comparator does not raise any objections.

Description of the proposed intervention

Tafamidis is a selective stabiliser of transthyretin (TTR). It binds to TTR at thyroxine binding sites, stabilising its tetramer and slowing dissociation to monomers, which limits the rate of amyloidogenesis.

Vyndaqel 61 mg tafamidis is recommended for the treatment of hereditary or wild-type transthyretin amyloid cardiomyopathy (ATTR-CM) in adult patients.

A dose containing 61 mg of tafamidis free acid form is bioequivalent to 80 mg of tafamidis meglumine (MegT).

Vyndaquel was granted orphan drug status for the treatment of senile systemic amyloidosis (also known as wild-type transthyretin amyloidosis).

The proposed indication is included in the registration indication.

Efficacy, effectiveness and safety assessment

This assessment involves collecting data on the health consequences (efficacy and safety) of the new therapy for the health problem in question and of other therapies that are currently reimbursed from public funds and represent alternative therapies available for the health problem. Furthermore, this assessment requires determination of the reliability of data collected and a comparison of the efficacy and safety results of the new therapy against the therapies already available to treat the health problem in question.

On the basis of the above, the efficacy and safety assessment allows answering the question of the scale of the health outcome (both in terms of efficacy and safety) to be expected from the new therapy compared with other therapeutic options under consideration.

The ATTR-ACT randomised clinical trial (RCT) with an additional extended trial (LTE) comparing the efficacy and safety of 80 mg and 20 mg doses of tafamidis meglumine (MegT) with placebo (PLC) was presented in the clinical analysis. As part of the LTE phase, after 20 July 2018, changes were introduced into the study protocol, as a result of which all patients received tafamidis 61 mg instead of MegT. Based on the Lockwood 2020 study, a dose of 61 mg tafamidis was considered bioequivalent to a dose of 80 mg tafamidis meglumine.

The population consisted of adults with ATTRwt or ATTRm cardiomyopathy and confirmed amyloid deposits based on the analysis of biopsy samples (N = 441). A dose of 80 mg MegT was given to 176 patients, while PLC was given to 177 patients. In the arm taking 80 mg MegT, the average age of patients was 75.2 ± 7.2 years (median – 76 years), while in the PLC arm, the average age was 74.1 ± 6.7 years (median – 74 years).

Efficacy

The analysis with the use of the Finkelstein-Schoenfeld method was performed, taking into account all-cause mortality and the number of hospitalisations due to cardiovascular issues, for the subgroup taking 80 mg of the drug, proving a statistically significant advantage of MegT over PLC (p=0.0030). The overall mortality rate was 30.7 vs 42.9%. The application of MegT compared to PLC was associated with a statistically significant reduction in overall mortality (HR = 0.690; 95% CI: 0.487-0.979; p=0.0378). The frequency of hospitalisations due to cardiovascular issues was 0.49 vs 0.70 per year and was also statistically significantly lower for the 80 mg MegT subgroup (RR = 0.70; 95% CI: 0.57-0.85; p=0.0005).

The least squares mean for slowing disease progression, measured as a distance covered while walking for six minutes, for the 80 mg MegT subgroup vs PLC was 75.77 ± 10.08 metres, p <0.0001. Considering that the change from 14.0 to 30.5 m may be clinically significant (Bohannon 2016), it was concluded that the difference in outcomes achieved with tafamidis meglumine treatment compared to the PLC group was statistically and clinically significant.

The least squares mean for a change in quality of life, according to the KCCQ-OS result analysis for the 80 mg MegT subgroup vs PLC subgroup, was 13.48 ± 2.20 points. A change of 5 points is assumed to be small but clinically significant, while changes of 10 and 20 points are considered to be clinical changes of medium to high and high to very high significance (Spertus 2020). For the comparison of the efficacy of tafamidis meglumine vs placebo, for the endpoint associated with the change in the KCCQ - OS score, the score can be considered of moderate clinical significance.

Safety

The full-text publication did not include results of the intervention consistent with the application, that is why the results published at clinicaltrials.gov and in the publication that also included results for the extended phase (LTE) are quoted.

Overall adverse events (AEs) were reported 2,138 times in the MegT 80 mg subgroup and 2,463 times in the PLC subgroup. The proportion of patients in the case of which there was a correlation between the occurrence of AEs and treatment was 44.9% in the MegT 80 mg subgroup and 50.8% in the PLC subgroup. The proportion of patients with at least one AE was 98.3% in the MegT 80 mg subgroup and 98.9% in the PLC subgroup. The safety profile of tafamidis meglumine used in the ATTR-ACT study is comparable to that of placebo.

It was similar in the LTE phase (data available for additional 12 months of treatment, median follow-up – 36 months) compared with results from the main phase of the ATTR-ACT study. Two hundred and twenty-seven patients were eligible for safety assessment in the combined analysis. The incidence of adverse events was lower, although considered comparable, 69.6%, due to incomplete data, similarly to the incidence of serious adverse events, 53.3%, and the proportion of patients who discontinued treatment - 17.6%. There were no patients who required a dose reduction due to the occurrence of adverse events.

Additional efficacy and safety information

Safety information based on WHO

The WHO website included information on the most common adverse events during treatment with Vyndaqel. To date, adverse effects have been reported in 2,769 patients. The highest number of the effects was reported in 2021 – 1,238. The majority of the effects were reported
for men (74%).

Limitations

The presentation of combined results for the 20 and 80 mg doses of tafamidis meglumine in the main publication related to RCT ATTR-ACT is a significant limitation. Attention should also be drawn to the fact that mostly older patients take the dose of 80 mg compared to patients taking 20 mg (median 76 vs. 73.5 years; p=0.0405), which may affect the conclusions and point to a lower randomisation efficacy. Differences were also noted in women, with the number being similar for the 80 mg MegT and PLC subgroups but being twice as low for the subgroup taking 20 mg MegT.

Other limitations are presented in the Agency Verification Analysis.

Proposed risk-sharing scheme [information protected as a trade secret]

Economic evaluation, including a cost-effectiveness estimation

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with the administration of the new therapy to an individual patient instead of already reimbursed therapies.

The costs of therapy are estimated in Polish currency, and health outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years (QALY) as a result of the therapy.

Juxtaposing the values concerning the costs and outcomes of a new therapy and comparing them to the costs and outcomes of already reimbursed therapies allows answering the question of whether

the health outcome achieved in an individual patient owing to a new therapy is associated with a higher cost in comparison with already reimbursed therapies.

The obtained results of the cost-effectiveness ratio are compared with the so-called cost-effectiveness threshold, i.e. a result that indicates that given the wealth of Poland (expressed in GDP), the maximum cost of the new therapy that is expected to produce a unit of health outcome (1 LYG or 1 QALY) compared to already available therapies should not exceed three times GDP per capita.

Currently, the cost-effectiveness threshold is PLN 166,758 (3 x PLN 55,586).

The cost-effectiveness ratio does not estimate or determine the value of life, but it only enables its assessment and the use of this assessment to choose the therapy associated with the potential best use of the currently available resources.

As part of the economic analysis, *cost-utility analysis* was conducted to compare the application of Vyndaqel (tafamidis) to the application of placebo (PLC). The analysis was performed for patients with ATTR-CM [information protected as a trade secret].

According to the applicant's estimates, the use of Tafamidis instead of placebo is [information protected as a trade secret]. The estimated ICUR was [information protected as a trade secret]. The values are [information protected as a trade secret] the cost-effectiveness threshold referred to in the Reimbursement Act.

With the ICUR estimated in the revised basic analysis, the net sales price of the drug at which the cost of an additional quality-adjusted life year is equal to the threshold value referred to in Art. 12 point 13 and Art. 19 sec. 2 point 7 of the Act is [information protected as a trade secret]. The estimated threshold value is [information protected as a trade secret].

The applicant presented a one-way sensitivity analysis, scenario analysis and probabilistic analysis. The one-way analysis assessed the outcomes after changing model parameters by an arbitrary value of ±20%, while the scenario analysis assessed parameters such as dosage intensity, heart transplants or zero discount rates [information protected as a trade secret]

Limitations

The verification of the structural correctness of the applicant's model did not show any limitations that significantly affect the reliability of the results presented by the applicant.

Indication whether the circumstances referred to in Art. 13 sec. 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021 item 523 as amended) do arise.

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed, the official selling price of the drug must be calculated so that the cost of the drug to be reimbursed is not higher than the cost of the health technology with the most favourable cost–effectiveness ratio.

Given the presentation of the randomised clinical trial proving the superiority of the assessed technology over the accepted comparator, the circumstances referred to in Art. 13 of the Reimbursement Act do not arise.

Assessment of the impact on the healthcare system, including the budget impact

Healthcare system impact assessment has two major parts.

First, the analysis of the impact on the payer's budget allows estimating the potential expenses associated with public reimbursement of the new therapy.

Estimates of the expenses associated with the new therapy (the "tomorrow" scenario) are compared to how much is currently spent on treating the health problem (the "today" scenario). On this basis, it

is possible to assess whether a new therapy will require more resources allocated to the treatment of the given health problem or whether it will result in savings in the payer's budget.

A budget impact assessment determines whether a payer has adequate resources to reimburse a particular technology.

Healthcare system impact assessment in the second part answers the question of how the decision on the reimbursement of a new therapy may affect the organisation of the provision of services (particularly in terms of adaptation to the requirements of the implementation of the new therapy) and the availability of other healthcare services.

The budget impact analysis was performed for a two-year time horizon. The analysis was performed from the public payer (NHF) perspective. The results for the joint perspective (NHF + patient) are the same as the results for the NHF perspective. The analysis considered two scenarios - the existing one and a new one. In the existing scenario, the treatment of patients with ATTR-CM was assumed to be symptomatic treatment of heart failure. The new scenario assumed that tafamidis would be financed from public funds under a new drug programme and within a new limit group.

The size of the target population in the 1st year was estimated to be [information protected as a trade secret], and for the 2nd year, it was [information protected as a trade secret].

The reimbursement of Vyndaqel will result in a significant increase in the expenditure of the entity obliged to finance the interventions from public funds in each of the variants of the analysis (possible, minimum and maximum). In the variant without the RSS, the total expenditure in the target population will increase in the probable variant (minimum, maximum) [information protected as a trade secret] in the 1st year of the reimbursement and [information protected as a trade secret] in the 2nd year of the reimbursement. Incremental expenses, when the RSS is considered, will be [information protected as a trade secret] in the 1st year of the reimbursement and [information protected as a trade secret] in the 2nd year of the reimbursement.

As part of the sensitivity analysis, the impact of changes in the values of parameters related to future population estimates on cost estimates was assessed. The sensitivity analysis was presented for the minimum and maximum variant at the same time. Two variants of the mortality rate, determined with the use of Kaplan-Maier curve in the ATTR-ACT study, were applied to the basic and minimum scenarios. For the maximum variant of the population, the mortality was assumed to be zero in the sensitivity analysis.

Limitations

Limitations were presented in the Agency Verification Analysis.

Comments on the proposed risk-sharing scheme [information protected as a trade secret]

Comments on the drug programme

The drug programme requires [information protected as a trade secret]

Attention is drawn to the proposed name of the drug programme in the case of which the ICD-10 code is assigned as E85, which is inconsistent with the indication that is the name of the drug programme. The correct identification code, which is the subject of the application according to the classification, should be I43.1, which fully corresponds to the assessed one. Code I43 is marked with an asterisk, which means that it should be reported along with E85 specifying which metabolic disease is involved.

Discussion on the solutions proposed in the rationalisation analysis

The subject of the rationalisation analysis is the identification of a mechanism, the introduction of which will result in the release of public funds in an amount corresponding to at least the increase in costs resulting from a positive decision on the reimbursement of the health technology covered in this recommendation.

The rationalisation analysis is submitted if the budget impact analysis for the entity responsible for funding indicates an increase in reimbursement costs.

In the analysis, the possibility of lowering the financing limit was considered, which will result from placing cheaper equivalents of the currently used substances on the market. Due to the inability to release funds in the desired amount from the products used in the proposed indication, the analysis considered the possibility of releasing the funds within the market of other pharmacotherapeutic groups. [information protected as a trade secret]

Overview of recommendations in relation to the assessed technology

Clinical recommendations

According to the existing clinical recommendations, patients with cardiac amyloidosis are recommended standard therapies to treat heart failure and/or arrhythmias. With that said, there is limited evidence on clinical benefits of ACEIs, ARBs, ARNIs, and β-blockers in the treatment of HF. All presented recommendations demonstrate the benefits of using disease-modifying drugs, i.e. tafamidis, patisiran and inotersen.

Tafamidis is a drug that turned out to be effective in the randomised trial that involved patients with ATTRwt and ATTRh with cardiomyopathy. The efficacy of patisiran and inotersen was confirmed in patients with polyneuropathy ± ATTRh cardiomyopathy.

Reimbursement recommendations

Considering the reimbursement of Vyndaqel (tafamidis) in the treatment of transthyretin amyloid cardiomyopathy, three positive recommendations (HAS 2020, PHARMAC 2019 and CADTH 2020) and 4 negative recommendations (SMC 2021, Zorginstituut 2021, NICE 2021 and NCPE 2020) were identified. The Canadian CADTH issued a positive recommendation provided that the price of the drug is reduced, while PHARMAC recommends financing tafamidis therapy with a medium priority. The positive recommendations mainly point to the lack of financing of alternative pharmaceuticals modifying the course of the disease, significant clinical benefits and a favourable ratio of drug efficacy to adverse effects. The negative recommendations mainly highlight the lack of cost-effectiveness and the inconsistent results on the efficacy of tafamidis in different types and stages of ATTR-CM.

According to the information provided by the applicant, Vyndaqel is financed [information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared based on the order of the Minister of Health of 5 October 2021 (ref. no.: PLR.4500.860.2021.18.AJA) concerning the preparation of the President's recommendation on the assessment of Vyndaqel (tafamidisum), 61 mg, 30 soft capsules GTIN 05415062359426 in the indication for use under the drug programme "Treatment of transthyretin amyloid cardiomyopathy with tafamidis in adults (ICD-10 E85)" pursuant to Art. 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021 item 523 as amended), having received Position of the Transparency Council No. 143/2021 of 20 December 2021 on the assessment of Vyndaqel (tafamidisum) under the drug programme "Treatment of transthyretin amyloid cardiomyopathy with tafamidis in adults (ICD-10 E85)".

References

1. Position of the Transparency Council No. 143/2021 of 20 December 2021 on the assessment of Vyndaqel (tafamidisum) under the drug programme "Treatment of transthyretin amyloid cardiomyopathy with tafamidis in adults (ICD-10 E85)".
2. Report No. OT.4231.49.2021: "Application for the reimbursement and establishment of the official selling price of Vyndaqel (tafamidis) under the drug programme for treatment of transthyretin amyloid cardiomyopathy with tafamidis in adults (ICD-10 E85) Verification Analysis" of 7 December 2021.