Recommendation No. 19/2020

of 27 February 2020

issued by the President of the Agency for Health Technology Assessment and Tariff System

on whether Nexavar (sorafenib) should be reimbursed in the following indication: "Treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/oxyphilic – Hürthle cell) thyroid cancer, refractory to radioactive iodine (ICD10 C73)"

The President of the Agency recommends reimbursing the following medicinal product: Nexavar (sorafenib), film-coated tablets, 200 mg, 112 tablets, EAN: 05909990588, in the following indication: "Treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/oxyphilic – Hürthle cell) thyroid cancer, refractory to radioactive iodine (ICD10 C73)" **provided that** the conditions offered in the risk-sharing scheme are enhanced or expanded.

Statement of reasons for the recommendation

Taking into account the position of the Transparency Council, the available scientific evidence, clinical guidelines and reimbursement recommendations, the President of the AOTMiT believes that financing of the health technology in question from public funds is justified, provided that the conditions offered in the risk-sharing scheme proposed by the applicant are enhanced or expanded.

In the absence of a currently available alternative treatment in the population in question, best supportive care (BSC) was selected as the comparator used in the analyses.

It should be noted that the search conducted for the present clinical analysis did not identify any additional randomised trials on sorafenib therapy published after the search conducted in the course of an analysis for Recommendation no. 9/2015. Nevertheless, two identified publications – Worden 2015 and Brose 2016 (an abstract) complement the safety profile of sorafenib and update the data on overall survival collected from the longer observation period of the DECISION study, on which the clinical analysis was based. The primary endpoint assessed in the study was PFS (progression-free survival). Findings of the study indicate an increase in median PFS by approx. 5 months in the SOR arm compared to the PLC arm, which was associated with a statistically significant difference in favour of SOR. Overall survival (OS) was assessed as one of the secondary endpoints. However, no results related to median OS were presented as part of the clinical analysis. Due to the fact that the trial was unblinded and sorafenib treatment was initiated in patients from the control arm when a patient progressed, statistical methods adjusting the cross-over effect were used. In line with the RPSFT (rank preserved structure failure time) method, higher probabilities of longer OS in the sorafenib arm were observed at various time points of the analysis. However, it should be noted that this is not a result of the basic analysis and it entails a certain risk of error. Therefore, drawing conclusions based on the above data is limited and does not allow for drawing a clear-cut conclusion regarding the efficacy of sorafenib in comparison to placebo in terms of OS prolongation. In addition, the studies, the results of which were

included in the clinical analysis and suggest the efficacy of the drug technology in question, are characterised by lower quality.

A utility cost analysis was carried out as part of the economic analysis; its results indicate *[information protected as a trade secret]*. The most important limitation of the economic analysis is the fact that it was based on OS results of the clinical analysis, which do not constitute reliable data. Considering the above, the conditions offered in the risk-sharing scheme should be significantly enhanced or should be expanded by additional mechanisms. Given the limitations related to efficacy and the assumptions of the economic analysis, it is reasonable to consider including a performance-based risk-sharing scheme.

The budget impact analysis indicates an increase in the public payer's expenses by *[information protected as a trade secret]* in the first year and by *[information protected as a trade secret]* in the second year of reimbursement, taking into account the risk-sharing scheme.

Clinical guidelines indicate the validity of the use of sorafenib in the proposed indication, at the same time indicating the possibility of using a different drug technology – lenvatinib – currently not financed from public funds.

The President of the Agency, taking into account the severe course of the disease and the lack of available alternative treatment, despite numerous limitations of the clinical and economic analyses, considers the financing of Nexavar (sorafenib) as justified in the following indication: progressive, locally advanced or metastatic, differentiated thyroid cancer, refractory to radioactive iodine (ICD10: C73), *[information protected as a trade secret]*.

Subject of the application

The order of the Minister of Health concerns assessing whether the following medicinal products should be financed from public funds:

- Nexavar (sorafenib), film-coated tablets, 200 mg, 112 tablets, EAN: 05909990588, with the proposed net ex-factory price: PLN 640.50; in the following indication:

"Treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/oxyphilic – Hürthle cell) thyroid cancer, refractory to radioactive iodine (ICD10 C73)".

The proposed payment and reimbursement availability category: a free-of-charge drug available as part of a drug programme, within the 1078.0 Sorafenib joint-limit group. The applicant has proposed a risk-sharing scheme.

Health problem

Thyroid cancer is a malignant tumour originating:

- from thyroid follicular cells:
    - differentiated thyroid cancers (DTC),
        - papillary thyroid cancers (PTC),
        - follicular thyroid cancers (FTC),
        - Hürthle cell carcinoma (HCC),
    - undifferentiated cancer (anaplastic – 2-5%),
- from calcitonin-producing C-cells (peridicular),
    - medullary cancer (5%).

The clinical presentation of thyroid cancer is unspecific. A developing nodule does not differ from benign nodules, therefore early diagnosis is only possible through fine-needle aspiration biopsy (FNAB). Lymph node metastases are more common in Hürthle cell tumours compared to FTC.

In some cases, the first noticeable symptom of the disease are cervical lymph nodes enlarged due to metastases. In about 5% of cases, distant metastases have already occurred, and they can be the first symptoms leading to the diagnosis.

Rapid growth of the nodule, its impermeability on the skin or hoarseness (a sign of infiltration of the laryngeal nerve) occurs at an advanced stage.

Thyroid cancer is the most common malignant tumour of the endocrine glands. Its incidence is about 7.4 in women and 1.7/100,000/year in men. The onset of the disease may occur at any age, peaking between 40 and 50 years of age. The number of thyroid cancer cases according to the KRN [National Cancer Registry] data for 2015 was 3,529 patients, of which about 605 were men and 2,924 were women. Over the past two decades, the number of cases has increased significantly.

According to data available on orphan.net, differentiated thyroid cancer (DTC) is the most common thyroid cancer. The annual incidence of this type of cancer is 1/10,000 residents. Iodine-refractory cancer affects 2/3 of patients with distant metastases who did not achieve a complete response during iodine therapy. This condition is extremely rare and affects 4-5 patients in 1 million (about 250 people per year in France).

The natural course of thyroid cancer has a positive prognosis if the treatment is commenced at an early stage (95-98% of patients survive at least 5 years). While in most cases differentiated thyroid cancer is treatable, locally advanced or metastatic cancer or cancer refractory to radioactive iodine (RAI) is more resistant and is associated with shorter patient survival, of up to 2.5–3.5 years. About 5-15% of patients become refractory to RAI therapy, 66% survive 5 years and 10% survive approx. 10 years. The prognosis for differentiated thyroid cancers (DTCs) is better in younger patients.

The growth of differentiated cancers is slow, which can lead to a false belief that the nodule is benign. Approximately 5% of patients are diagnosed at a late stage, in the generalised dissemination phase, when the prognosis is worse and despite treatment, only approx. 50% of patients survive 10 years. The formation of non-iodine avid distant metastases is particularly unfavourable.

Alternative health technologies

Based on the identified guidelines and the opinions of clinical experts, best supportive care was selected as the alternative therapy to sorafenib.

In line with the opinion of the expert cited by the applicant, currently the analysed patient population is treated with BSC, which includes thyroid hormone therapy, bisphosphonates, analgesics and corticosteroids, as well as palliative radiotherapy.

Description of the proposed intervention

The active substance of the product in question – Nexavar – is sorafenib, available in the form of film-coated tablets, 200 mg per dose.

Sorafenib is a multi-kinase inhibitor which reduces tumour cell proliferation in vitro. It inhibits the growth of various human cancerous tumours in a mouse model of renal cell carcinoma, which is accompanied by a reduction in tumour angiogenesis. Sorafenib inhibits the activity of target enzymes/factors located in the tumour cell and in the tumour vasculature.

In line with the Summary of Product Characteristics, Nexavar is indicated in the treatment of:

- hepatocellular carcinoma;

- patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy;
- patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

Efficacy, effectiveness and safety assessment

The assessment consists in the collection of data on health consequences (efficacy and safety) resulting from the use of a new therapy in a given health problem and other publicly financed therapies which constitute an alternative treatment option available in a given health problem. Then, the assessment requires determining the reliability of the collected data and comparing the results regarding the efficacy and safety of the new therapy with those of therapies already available in a given health problem.

Based on the above, the efficacy and safety assessment allows for obtaining information about the extent of the health effect (with regard to both efficacy and safety) to be expected in relation to the new therapy compared to the other considered therapeutic options.

It should be noted that the applicant's clinical analysis includes studies and reviews presented also in the framework of analysis No. AOTM-OT-4351-41/2014 of 2014, in which the use of sorafenib in differentiated thyroid cancers (including papillary, follicular, oxyphilic – Hürthle cell cancer) was assessed. The analysis has been updated by way of including the following systematic reviews: Yu 2019, Fleeman 2019, Donato 2018, Yang 2017, Kawalec 2016, Gruber 2015, Blair 2015, Yang 2015, Hesselink 2015 and McFarland 2014.

All secondary studies were assessed using the AMSTAR 2 scale. All the included systematic reviews with a meta-analysis (7/7) received a critically low rating. Of all the systematic reviews without a meta-analysis, one was characterised by low quality, while the remaining ones (9/10) received a critically low rating.

No additional RCTs (randomized controlled trials) for sorafenib therapy published after the search of AOTM-OT-4351-41/2014 were identified. At the same time, the results presented in Worden 2015 and Brose 2016 included in this study, respectively complement the data on the safety profile of sorafenib and update the overall survival data from the longer observation period of the DECISION study.

Primary studies:

- DECISION (Schlumberger 2013, Brose 2014, abstract: Brose 2014a, Brose 2016, NICE 2017) – a phase III multi-centre, double-blind RCT.
    - Intervention and patient population:
        - Study arm: sorafenib (SOR) – 207 patients;
        - Control arm: placebo (PLC) – 210 patients.
    - Analysis period: main analysis – median of 16.2 months (range: 0.03-33.2);
    - The quality of the test was assessed using, among others, the Cochrane Collaboration tool:
        - Low risk of bias was determined in the following areas: randomisation method, concealment of the randomisation code, blinding of participants and personnel, blinded outcome assessment and incomplete data;
        - Unclear risk of bias was determined in the area of selective reporting and other factors.

          According to the applicant, the DECISION study is characterised by a low risk of bias in all the assessed areas. According to the Agency, blinding of investigators and patients is associated with a low risk of bias only in the double-blind phase. It should be noted that, after the investigator diagnosed progression, the treatment was unblinded and patients from the placebo or sorafenib arm could receive sorafenib

in the open phase of the study (cross-over), which could have largely influenced the increased risk of bias.

In addition, in the Agency's opinion, due to the lack of reporting on the quality of life results in the full-text publication and the fact that the DECISION study was sponsored by a MAH, the risk in the area of selective reporting and other factors can be described as unclear.

The applicant also included 20 non-randomised, uncontrolled trials described in 21 publications in the review: Ahmed 2011, Benekli 2014, Bugalho 2016, Capdevila 2012, Chrisoulidou 2015, Dadu 2014, Gallo 2015, Gupta-Abramson 2008, Hoftijzer 2009 (described in Hoftijzer 2009 and Schneider 2012), Jerkovich 2019, Kim 2018, Kim 2019, Kim 2019a, Kloos 2009, Luo 2014, Marotta 2013, Marotta 2017, Massicotte 2014, Molina-Vega 2018 and Pitoia 2014. Ahmed 2011, Gupta-Abramson 2008, Hoftijzer 2009, Schneider 2012, Kloos 2009 and Pitoia 2014 were also included in the 2014 verification analysis. Taking into account the fact that higher-quality evidence which assessed the most important endpoints are available, it was decided that their results would not be presented.

All the included studies were of moderate/good quality, scoring 3-7 points out of 8 possible on the NICE scale.

The following scales and questionnaires were used in the clinical analysis:

- FACT-G (Functional Assessment of Cancer Therapy – General) – the questionnaire contains questions concerning the following areas: physical, family/social, emotional and functional well-being. Answers to the questions are given in line with the Likert scale, from 0 to 4, and the total possible score is 28. The lower the score, the lower the quality of life. An increase by ≥ 4 points indicates a better response, while points from -3.99 to 3.99 indicate the same response. A decrease by 4 points or more indicates deterioration;
- EQ-5D (Euro QoL – 5 dimensions) and EQ VAS (Euro QoL visual analogue scale) – instrument for assessing health, designed in a way which allows it to be filled in by the patient. The descriptive EQ-5D concerns the following dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The severity of each dimension can be assessed on a 3-point scale: 1 – no problem, 2 – moderate problem, 3 – extreme problem. EQ VAS is a standard 20-centimetre, vertical visual analogue scale of 0-100 (similar to a thermometer) for recording individual graphical assessment of a respondent concerning his/her current health-related quality of life.

The following parameters were used to assess efficacy:

- HR – hazard ratio; relative likelihood of an event occurring in the study arm and the control arm at any time point;
- MD – mean difference;
- RR – relative risk; risk ratio in the study arm in relation to the risk in the control arm;
- RD – risk difference; risk difference in the study arm and control arm;
- NNT (Number Needed to Treat) – number of people in whom the assessed intervention should be used instead of the comparator to obtain an additional occurrence or to avoid the occurrence of the given event within a specified time horizon.
- NNH (Number Needed to Harm) – number of patients in whom the use of a specific intervention for a specific period of time is associated with the occurrence of one additional adverse endpoint or the absence of one beneficial endpoint.

In the efficacy analysis, the following endpoints were assessed:

- OS – overall survival;
- PFS – progression-free survival;

- TTP – time to progression;
- ORR – objective response ratio;
- CR – complete response;
- PR – partial response;
- SD – stable disease;
- DCR – disease control rate.

Efficacy

Overall survival (OS)

Due to the possibility of unblinding both study arms and using sorafenib in the control arm in the event of an identified disease progression, two statistical methods adjusting for the cross-over effect were used: RPSFT (rank preserved structure failure time) and IPE (iterative parameter estimation).

As part of the post-hoc analysis, a lower risk of death was observed in the sorafenib arm in comparison with the placebo arm (calculated using the RPSFT method):

- by 39% in the main analysis: HR = 0.61 (95% CI: 0.40; 0.94);
- by 31% in first update: HR = 0.69 (95% CI: 0.49; 0.99).

In the main analysis, the median overall survival was not achieved in any of the treatment arms for a median observation period of 16.2 months.

No statistically significant difference was noted between the sorafenib arm and the placebo arm in terms of overall survival in the absence of a cross-over correction method.

In the latest update of the overall survival analysis reported in Brose 2016 (cut-off date: July 2015), no statistically significant differences were reported both in the primary unadjusted analysis and after adopting adjustment methods (IPE and RPSFT).

At the same time, it should be noted that as at the cut-off date, 158/210 (75%) of the patients in the placebo group had started sorafenib treatment due to disease progression, which may significantly distort the obtained results.

The authors of Brose 2016 also indicated that the separation of Kaplan-Meier curves was maintained in time in favour of sorafenib (however, the graphs were not presented in the abstract). The analysis including adjustment due to the use of the cross-over method indicated higher efficacy of sorafenib treatment than the analysis carried out in line with the ITT (intention to treat) methodology.

Progression-free survival (PFS)

Differences in PFS in favour of the SOR arm compared to the arm using PLC were noted for a median observation period of 16.2 months:

- As assessed by an independent committee, median PFS in the arm using SOR (median = 10.8 months) was 5 months longer than in the arm using PLC (median 5.8 months). A statistically significantly lower risk of progression (by 41%) in the SOR arm compared to the PLC arm was recorded: HR = 0.59 (95% CI: 0.45; 0.76);
- As assessed by the researchers, median PFS in the SOR arm (median = 10.8 months) was 5.4 month longer than in the PLC arm (median = 5.4 months). A statistically significantly lower risk of progression (by 51%) in the SOR arm compared to the PLC arm was recorded: HR = 0.49 (95% CI: 0.39; 0.61).

Depending on the histopathological type of differentiated thyroid cancer, a significantly statistically lower risk of progression was reported in sorafenib users compared to patients using placebo in the subgroup:

- Patients with papillary cancer, 43% lower – HR = 0.53 (95% CI: 0.37; 0.75);

- Patients with oxyphilic cancer, 56% lower – HR = 0.44 (95% CI: 0.25; 0.78);

No statistical significance was achieved in the subgroup of patients with follicular cancer.

Time to progression (TTP)

A 5.4 month longer median TTP was noted in the sorafenib arm (median = 11.1 months) compared to the PLC arm (median = 5.7 months). The risk of shorter TTP was statistically significantly lower by 44% in the arm using SOR vs PLC: HR = 0.56 (95% Cl: 0.43; 0.72).

Quality of life

The assessment of the quality of life in patients from the DECISION study was presented in Schlumberger 2013; the Agency also took into account data from the EUnetHTA 2015 report.

Statistically significant differences to the disadvantage of sorafenib were noted in the quality of life assessment questionnaires:

- FACT-G: MD = -3.45 (95% Cl: -5.45; - 2.20);
- EQ-5D: MD = -0.07 (95% Cl: -0.10; 0.04);
- EQ-5D VAS: MD = -6.75 (95% Cl: -9.38; -4.13).

Taking into account the NICE 2017 report, which indicates 0.10 to 0.12 point-changes on the EQ-5D scale and at least 7-point changes on the EQ-5D VAS scale as statistically significant, the obtained results should be considered clinically irrelevant.

The minimum clinically relevant difference for the FACT-G questionnaire results reported in the NICE 2017 report is -3 to -7, thus indicating that the result obtained in the FACT-G questionnaire reached the lower limit of clinical relevance (-3.45).

Response to treatment

For treatment response endpoints:

- over 24.5 times higher probability of ORR was noted in the SOR arm compared to the arm using PLC: RR = 24.61 (95% Cl: 4.31; 142.89), RD = 0.12 (95% Cl: 0.07; 0.1), NNT = 9 (95% Cl: 7; 15).

  Considering the fact that CR was not recorded, the PR results were equivalent to the ORR result.
- A 60% higher probability of DCR was noted in the SOR arm compared to the PLC arm: RR = 1.60 (95% Cl: 1.27; 2.02), RD = 0.20 (95% Cl: 0.11; 0.30), and NNT=5 (95% CI: 4; 10).

No statistically significant differences were noted in terms of achieving SD, defined as stable disease lasting for at least 4 weeks.

Safety

The DECISION safety assessment was based on events reported in the double-blind phase of all randomised patients who received at least one dose of sorafenib. The median treatment period was 10.6 months in the sorafenib arm and 6.5 months in the placebo arm.

Deaths

No statistically significant differences were noted in terms of incidence of death in the arm of patients treated with sorafenib compared to the placebo arm.

The percentage of treatment-emergent adverse events (TEAEs) was:

- 5.8% (12 patients) in the sorafenib arm;
- 2.9% (6 patients) in the placebo arm;

The cause of 7 deaths in the sorafenib arm was cancer, in 2 the cause was not determined, while in the remaining 3 cases the cause of death was pneumonia, chronic obstructive pulmonary disease and myocardial infarction. In each arm, one death was considered to be treatment-emergent – a death due to myocardial infarction in the sorafenib arm and a death due to subdural haematoma in the placebo arm.

Adverse events (AEs)

A statistically significant, 13% higher risk of overall adverse reactions was noted in the sorafenib arm (98.6%) compared to the placebo arm (87.6%): RR = 1.13, 95% CI: 1.07; 1.20); NNH=10 (95% Cl: 7; 16).

In addition, patients treated with sorafenib compared to the placebo arm have the following statistically significant risks of:

- 41% greater risk of severe adverse events (total): RR=1.41 (95% CI: 1.06; 1.89), NNH= 10 (95% Cl: 6; 52);
- over 2.5 times greater risk of suspending treatment due to AEs: RR=2.56 (95% CI: 2.01; 3.31), NNH=3 (95% Cl: 3; 4);
- almost 5 times greater risk of discontinuing treatment due to AEs: RR=4.92 (95% CI: 2.41; 10.16), NNH=7 (95% Cl: 5; 11);
- over 7 times greater risk of reducing the dose due to AEs: RR=7.07 (95% CI: 4.61; 11.02), NNH= 2 (95% Cl: 2; 3).

The most frequently reported serious adverse events occurring in ≥2% of patients in the SOR arm were secondary cancer (3.4%), dyspnoea (2.9%), and pleural effusion (1.9%). No statistically significant differences in terms of incidence were indicated between the assessed intervention and the comparator.

The following grade 3 or 4 adverse events, for which statistically significant differences to the disadvantage of sorafenib compared to placebo were noted: hand-foot skin reaction, diarrhoea, rash or skin desquamation, fatigue, weight loss, hypertension, decreased appetite, hypocalcaemia and increased ALT activity.

The most commonly reported adverse events in the sorafenib arm were hand-foot skin reaction, diarrhoea, alopecia, rash/skin desquamation, fatigue, weight loss and hypertension. Hand-foot skin reaction was the most common reason for suspending sorafenib administration, reducing its dose and discontinuing treatment altogether. Aside from cough, back and limb pain and dyspnoea (for which no statistically significant differences were indicated between the arms), all the adverse events reported in >10% of patients occurred more frequently in the intervention arm.

Additional safety information

The SPC of Nexavar described the safety of use of Nexavar (200 mg of sorafenib) administered to patients with hepatocellular, renal cell carcinoma and differentiated thyroid cancer.

The SPC specified the following adverse reactions:

- very common adverse reactions (≥1/10): infections, lymphopenia, anorexia, hypophosphataemia, haemorrhage, hypertension, diarrhoea, nausea, vomiting, constipation, dry skin, rash, alopecia, hand-foot skin reaction, erythema, pruritus, arthralgia, fatigue, pain, fever, decreased weight, increased amylase and lipase;
- common adverse reactions (≥1/100-<1/10): folliculitis, leukopenia, neutropenia, anaemia, thrombocytopenia, hypothyroidism, hypocalcaemia, hypokalaemia, hyponatraemia, hypoglycaemia, depression, peripheral sensory neuropathy, dysgeusia, tinnitus, congestive heart failure, myocardial ischaemia and infarction, flushing, rhinorrhoea, dysphonia, stomatitis, dyspepsia, dysphagia, gastro oesophageal reflux disease, keratoacanthoma/ squamous cell cancer of the skin, dermatitis exfoliative, acne, skin desquamation, hyperkeratosis, myalgia, muscle spasms, renal failure, proteinuria, erectile dysfunction, asthenia, influenza like illness, mucosal inflammation, transient increase in transaminases.

The most severe adverse reactions are: myocardial infarction/ischaemia, gastrointestinal perforation, drug-induced hepatitis, bleeding and hypertension/hypertensive crisis.

The SPC for Nexavar indicated the following special warnings and precautions for use: dermatological toxicity, hypertension, hypoglycaemia, haemorrhage, myocardial ischaemia and (or) infarction, QT interval prolongation, gastrointestinal perforation, hepatic impairment, wound healing complications, drug-drug interactions.

The following alerts and information on the safety of sorafenib have been identified:

- FDA (Food and Drug Administration) – Sorafenib was designated as Most-DILI-concern drug, which is a drug with special warnings in terms of hepatotoxicity. In addition, the FDA updated the part of the SPC regarding the safety of Nexavar.
- EMA (European Medicines Agency) – information on signals of acute generalised exanthematous pustulosis have been found. The identified information was considered insufficient to establish a relationship between the use of sorafenib and this adverse event. In addition, information on reported aneurysm and artery dissection, which referred to sorafenib and other drugs exhibiting vascular endothelial growth factor receptor inhibitors have been found.

No announcements were found on the website of URPL (Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products).

Limitations

The most important limitation of the clinical analysis is the existence of cross-over in the DECISION study between patients in the sorafenib and placebo arms following progression observed in the placebo arm. Therefore, the study did not complete observation with regard to the overall survival endpoint, and thus median overall survival (OS) was not achieved.

The results of the OS analysis update are described in conference abstracts. However, no full-text publication reporting the above data is available. In addition, an OS analysis using cross-over correction methods was performed as part of the exploratory analysis, which increases the uncertainty of the obtained results.

Additionally, it should be noted that, according to the data presented in the NICE 2017 report assessing the efficacy of sorafenib in the analysed population, the median value of OS was determined.

The reliability of the clinical analysis is affected by the following limitations:

- Progression-free survival is the primary endpoint assessed in the DECISION study. It should be noted that no conclusive data were found to confirm the relationship between the PFS results and survival analysis results in the assessed population;
- In the DECISION study, patients were allowed to use other cancer treatments following disease progression, which may distort the results of the survival analysis;
- The DECISION study protocol allowed continued use of sorafenib even after disease progression, which could have affected the results of the OS analysis. [*information protected as a trade secret*] Therefore, in actual practice, the survival results may differ from those observed in the DECISION study.

The uncertainty of the clinical analysis is affected by the following limitations:

- The patient population included in the DECISION study did not fully match the population included in the drug programme. Patients qualified for the drug programme with papillary/follicular/Hürthle cell thyroid carcinoma refractory to radioactive iodine constituted 57%, 8% and 18% of patients included in the study, respectively, while poorly differentiated cancer patients constituted 10% of the study population. Considering the above, it is worth noting that the results for individual

subpopulations are presented only in the assessment of the primary endpoint (PFS). Other results were reported for the total study population;

- DECISION contains no full-text publications reporting results on the assessment of patients' quality of life. The data on the quality of life was assessed as part of the exploratory analysis, and the results were presented in a conference abstract (Schlumberger 2013), which affects the uncertainty of the obtained results.
- Given the low share of patients with follicular thyroid cancer in the DECISION study, the obtained results may not be fully representative of the population in question;
- The objective of the DECISION study was to assess the efficacy of sorafenib in the population of patients with metastatic and locally advanced differentiated thyroid cancer. And yet the occurrence of metastatic disease was reported in 96% of patients enrolled in the study. Therefore, data on the efficacy of sorafenib in patients with locally advanced cancer is significantly limited;
- *[information protected as a trade secret].* At the same time, DECISION mainly included patients whose ECOG performance status was 0 or 1. *[information protected as a trade secret];*
- The results of the subgroup analysis, due to the lack of relevant figures reported in the DECISION study, were derived from charts. Therefore, the results may be slightly different from the original data.

Proposals of risk-sharing schemes

[information protected as a trade secret].

Economic analysis, including a cost-effectiveness estimation

An economic analysis consists in estimating and comparing the costs and health effects which may be associated with the use of a new therapy in an individual patient instead of therapies which are currently reimbursed.

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

The comparison of values concerning the costs and effects related to the use of a new therapy and comparing them to the costs and effects of currently reimbursed therapies allow for obtaining an answer to the question on whether the health effect achieved as a result of the new therapy is associated with higher costs in comparison to the currently reimbursed therapies.

The achieved cost-effectiveness ratios are compared with the so-called cost-effectiveness threshold, i.e. which indicates that taking into account the means at the disposal of Poland (expressed in its GDP), the maximum cost of a new therapy necessary to obtain a unit of health effect (1 LYG or 1 QALY), compared to the currently available treatments, should not exceed three times the amount of per capita GDP.

Currently the cost-effectiveness threshold in Poland amounts to PLN 147,024 (3 x PLN 49,008).

The cost-effectiveness ratio does not estimate or determine the value of life, it only allows to assess and, among other things, select a therapy associated with the potentially best use of the currently available resources.

As part of the economic analysis, the applicant conducted an economic analysis in the form of a cost-utility analysis (CUA) from the public payer's perspective (the National Health Fund) and from the common perspective (the NHF and the patient), which is comparable to the payer’s perspective in terms of the conditions for reimbursement proposed in the application (i.e. drug programme).

The economic model includes the following costs: the cost of sorafenib, the cost of drug administration, diagnosis and monitoring of therapy under the proposed drug programme, the cost of routine care (BSC), the cost of non-drug services, and the cost of treating grade 3 and 4 adverse events for which statistically significant differences in incidence were observed. Discounting in the amount of 5% for costs and 3.5% for health effects was taken into account. A lifetime time horizon (30 years) was adopted.

According to the applicant's estimates from the NHF's perspective, the use of sorafenib with BSC in BSC is *[information protected as a trade secret]*. The estimated incremental cost utility ratio (ICUR) for the SOR vs BSC comparison was:

- PLN/QALY *[information protected as a trade secret]* taking into account the risk-sharing scheme (RSS);
- PLN 351,946/QALY without taking the RSS into account.

[information protected as a trade secret] of the profitability threshold referred to in the Act on reimbursement (PLN 147,024/QALY).

The net ex-factory price per packaging unit of Nexavar, for which the cost of obtaining one quality-adjusted life year (QALY) is equal to the assumed cost-effectiveness threshold (PLN 147,024), from the perspective of the NHF is:

- PLN *[information protected as a trade secret]* taking into account the RSS;
- PLN *[information protected as a trade secret]* without taking into account the RSS;

[information protected as a trade secret]

The conducted deterministic sensitivity analysis demonstrated that:

- In the variant taking the RSS into account:
    - the highest deviations to the disadvantage of sorafenib were found in the variants including the alternative HR parameter value for overall survival in the BSC arm:
        - upon adopting the HR from the final analysis, the overall survival ICUR values were *[information protected as a trade secret]*
        - taking into account cross-over adjustment using the IPE method – the ICUR value is *[information protected as a trade secret]*
    - The highest deviations in favour of the intervention in question were recorded in the scenarios testing the extrapolation of Kaplan-Meier curves from the DECISION study regarding overall survival, using alternative parametric distributions (log-normal and log-logistic) – the ICUR value *[information protected as a trade secret]* in relation to *[information protected as a trade secret]*
- This variant of the analysis not taking the RSS into account:
    - The highest deviations to the disadvantage of sorafenib were due to:
        - adopting the HR from the final survival analysis – this changes the ICUR value to PLN 491,000/QALY
        - taking into account cross-over correction using the IPE method – ICUR equal to PLN 544,000/QALY.
    - Deviations from the results of the basic analysis in favour of sorafenib resulted from the adoption of alternative parametric curves (log-normal, log-logistic) for overall survival – ICUR was PLN 190,000/QALY and PLN 195,000/QALY, respectively.

The conducted probabilistic sensitivity analysis indicates that, at the current cost-effectiveness threshold (PLN 147,024/QALY), the cost-effectiveness probability of sorafenib in the RSS variant is *[information protected as a trade secret]* and 2% in the variant without RSS.

[information protected as a trade secret]

Limitations of the analysis

The main limitation of the economic analysis is the significant uncertainty regarding the key parameter – overall survival – included in the economic model. The median overall survival in the DECISION study was not achieved and no differences between sorafenib and BSC in terms of this endpoint were found. The applicant's basic analysis is based on results adjusted for cross-over (which occurred in 75% of patients in the BSC arm) obtained as part of post-hoc secondary survival analyses. It should also be underlined that the applicant has not submitted scientific evidence showing a correlation between PFS and OS. Assuming that the applicant's model lacks differences in overall survival between the two compared arms, the intervention in question becomes a technology dominated *[information protected as a trade secret]*.

It should also be noted that the analyses adopted the HR value for overall survival based on an interim-analysis from the cut-off point in May 2013, despite the existence of more recent data for this parameter (cut-off point in July 2015). The applicant explains that this approach is caused by the inability to reproduce survival curves for more recent data. However, it should be borne in mind that this parameter significantly affects the results of the economic analysis – testing the adoption of an updated value of this parameter as part of the sensitivity analysis has shown *[information protected as a trade secret].*

Indication whether the circumstances referred to in Article 13, paragraph 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Journal of Laws No. 2017, item. 1844, as amended) occur;

In case the applicant's clinical analysis does not include randomised clinical trials which prove the superiority of the drug over the medical technologies which are currently reimbursed in the particular indication, it is the ex-factory price of the drug which must be calculated in such a way that the cost of using the drug applying for reimbursement is not higher than the cost of the health technology with the most favourable ratio of health effects to the cost of obtaining them.

Given the fact that randomised clinical trials demonstrating the superiority of the technology in question over the current practice (no treatment) have been presented, the circumstances specified in Article 13 of the Act on reimbursement do not occur.

Analysis of the effects on the healthcare system, including budget impact analyses (BIA)

The analysis of the effects on the healthcare system consists of two important parts.

Firstly, the analysis of the impact on the payer's budget allows for estimating potential expenditure related to the financing of a new therapy from public funds.

The estimated expenditure related to the new therapy (the "tomorrow" scenario) is compared with how much currently is spent on the treatment of a particular health problem (the "today" scenario). On that basis it is possible to assess whether the new therapy will require a higher level of funding for the treatment of a particular health problem or whether it will involve savings in the payer's budget.

The budget impact assessment makes it possible to determine whether the payer possesses the necessary resources to finance a particular technology.

The second part of the analysis of the effects on the healthcare system raises the question on how the decision to finance a new therapy can affect the organisation of the provision of services (especially in the context of adjustments necessary for the new therapy to be used) and the availability of other healthcare services.

As part of the budget impact analysis, the applicant has provided the estimates of the expected expenditure on the public payer's part in the case of adopting a positive decision on financing Nexavar (sorafenib) from

public funds used for the treatment of advanced, differentiated thyroid cancer, refractory to radioactive iodine.

The assessment of the impact on the public payer's budget was conducted from the NHF's perspective in a 2-year horizon. The estimated number of patients using the drug technology in question after issuing a positive reimbursement decision is:

- Year 1: 150 (min. 145 – max. 154);
- Year 2: 155 (min. 145 – max. 163).

The following costs were included in the analysis: the cost of sorafenib, drug administration under the programme, diagnosis and treatment monitoring, treatment of grade 3 and 4 events, routine care in the absence of progression, taking the costs of BSC (pharmacotherapy and medical services) into account, routine care in the case of progression, taking the costs of BSC and medical services into account, as well as palliative radiotherapy.

The introduction of financing for the technology in question will involve incremental costs from the NHF's perspective in the amount of:

- taking the proposed RSS into account:
    - PLN *[information protected as a trade secret]* in the first year of reimbursement;
    - PLN *[information protected as a trade secret]* in the second year of reimbursement;
- without taking the proposed RSS into account:
    - PLN 10,050,269 in the first year of reimbursement;
    - PLN 21,512,156 in the second year of reimbursement;

Sensitivity analysis

In the minimum variant, in the event Nexavar is reimbursed and no RSS is taken into account, the public payer's expenditure will increase by approx. PLN 9.7 million in the first year of reimbursement and by approx. PLN 20.4 million in the second year of reimbursement, and if the proposed risk-sharing scheme for Nexavar is taken into account, the public payer's expenditure *[information protected as a trade secret]*.

In the maximum variant, in the event Nexavar is reimbursed and no RSS is taken into account, the public payer's expenditure will increase by approx. PLN 10.3 million in the first year of reimbursement and by approx. PLN 22.3 million in the second year of reimbursement, and if the proposed risk sharing scheme for Nexavar is taken into account, the public payer's expenditure *[information protected as a trade secret]*.

As part of the sensitivity analysis, the applicant has also conducted a deterministic sensitivity analysis, in which it analysed the impact of factors, such as: a change in the price of sorefanib, changes in the cost of diagnostics in the drug programme, the duration of treatment determined by the PFS curve and the participation of radiation therapy in the current scenario. The conducted analysis showed that the results of the budget impact analysis were stable.

Limitations of the analysis

The applicant's analysis assumes that a steady number of patients from the target population in included in the programme in the subsequent months. Considering the unmet needs in this population and the fact that, currently, *[information protected as a trade secret*] are already treated with sorafenib under the Emergency Access to Drug Technologies (RDTL) procedure, the Agency recommends assuming that a significant proportion of patients will start sorafenib therapy in the first months following the reimbursement decision.

The additional limitations of the analysis are as follows:

- The applicant's model assumes a higher overall survival of patients using sorafenib vs placebo, which is not confirmed by the results of the clinical analysis. Nevertheless, the above assumption has a marginal impact on the public payer's part in the analysed horizon.
- Estimates of the target population based on expert opinions are uncertain, however there are no reliable epidemiological data that would ensure reliable calculations, and available epidemiological indicators suggest that these estimates may be close to the actual values.
- The budget impact analysis (BIA) used performance parameters and cost values estimated as part of the applicant's economic analysis, therefore the limitations of these assumptions apply also to the BIA.

Remarks on the proposed risk-sharing scheme

[information protected as a trade secret].

Remarks on the drug programme records

In line with the content of the drug programme approved in 2014, the patient should undergo a histological examination confirming the diagnosis. *[information protected as a trade secret].*

[information protected as a trade secret].

[information protected as a trade secret]

[information protected as a trade secret]

Review of the solutions proposed in the rationalisation analysis

The objective of the rationalisation analysis is to identify a mechanism which, if introduced, will result in a release of public funds in an amount at least corresponding to the increase in costs resulting from a positive decision to reimburse the intervention in question in the analysed indications.

A rationalisation analysis is submitted if the budget impact analysis of the public payer demonstrated that the cost of reimbursement would increase.

As part of the rationalisation analysis, the applicant proposed a solution allowing for generating savings for the public payer to cover additional expenditure associated with the reimbursement of Nexavar in the indication in question, in the basic and maximum variant, taking the RSS into account.

The proposed mechanism consists of: *[information protected as a trade secret].*

Implementing the solution proposed by the applicant was assessed as unlikely.

Review of recommendations issued in other countries in relation to the technology in question

7 clinical guidelines have been identified:

- Jarząb 2018 – Polish;
- European Thyroid Association (ETA) 2019 – Europe;
- European Society of Medical Oncology (ESMO) 2019 – Europe;
- National Comprehensive Cancer Network (NCCN) 2.2019 – United States;
- National Cancer Institute (NCI) 2018 – United States;
- American Thyroid Association (ATA) 2015 – United States;
- Italian Society of Endocrinology (SIE) 2018 – Italy.

All the guidelines point to sorafenib as the recommended or applicable therapy for the treatment of patients with progressive, locally advanced and/or metastatic thyroid cancer refractory to radioactive iodine. Also, guidelines published before 2014 (i.e. before the issuance of marketing authorisation for the drug registration in this indication) included in AWA AOTM-OT-4351-41/2014 (PUO 2013, NCCN 2013/2014, ESMO 2012, ATA 2009) indicated the possibility of considering sorafenib in the treatment of metastatic, progressive differentiated thyroid cancer, refractory to radioactive iodine.

Lenvatinib, with marketing authorisation in the above indication applicable throughout the European Union (central procedure) is mentioned, along with sorafenib, as a tyrosine kinase inhibitor used in first-line treatment. The latest American NCCN 2.2019 guidelines (National Comprehensive Cancer Network) define lenvatinib as the therapy preferred over sorafenib.

5 reimbursement recommendations for the use of Nexavar in thyroid cancer treatment have been identified:

- Haute Autorité de Santé (HAS) 2015 (France) – The organisation recommends reimbursement of Nexavar as part of the list of drugs issued by pharmacists and used in hospitals;
- Scottish Medicines Consortium (SMC) 2015 (Scotland) – Nexavar was approved for use within the Scottish NHS in patients with progressive, locally advanced or metastatic differentiated thyroid cancer refractory to radioactive iodine.
- National Institute for Health and Care Excellence (NICE) 2018 (United Kingdom) – positive recommendation on the use of lenvatinib and sorafenib in the treatment of progressive, locally advanced or metastatic differentiated (follicular, papillary or Hürthle cell) thyroid cancer in adult patients, refractory to radioactive iodine treatment, only if no treatment is applied or tyrosine kinase inhibitor therapy is discontinued;
- All Wales Medicines Strategy Group (AWMSG) 2018 (Wales) – Recommendation in line with the NICE 2018 recommendation;
- pan-Canadian Oncology Drug Review (pCORD) 2015 (Canada) – The pCORD experts do not recommend financing sorafenib in patients with locally advanced or metastatic differentiated thyroid cancer refractory to radioactive iodine.

[information protected as a trade secret].

Legal basis for the recommendation

The recommendation was prepared on the basis of an order of the Minister of Health of 28 October 2019 (reference numbers: PLD.4600.1345.13.2019.KK on whether Nexavar (sorafenib) should be reimbursed in the following indication: "Treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/oxyphilic – Hürthle cell) thyroid cancer, refractory to radioactive iodine (ICD10 C73)", pursuant to Article 35 paragraph 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional purposes and medical devices (Journal of Laws of 2019, item 784, as amended), after having read the Position of the Transparency Council No. 19/2020 of 24 February 2020 on the evaluation of Nexavar (sorafenibum) under the following drug programme: "Treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/oxyphilic – Hürthle cell) thyroid cancer, refractory to radioactive iodine (ICD10 C73)".

References

1. Position of the Transparency Council No. 19/2020 of 24 February 2020 on the evaluation of Nexavar (sorafenibum) under the following drug programme: "Treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/oxyphilic – Hürthle cell) thyroid cancer, refractory to radioactive iodine (ICD10 C73)"

2. Report No. OT.4331.62.2019 Nexavar (sorafenibum) under the following drug programme: “Treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/oxyphilic – Hürthle cell) thyroid cancer, refractory to radioactive iodine (ICD10 C73)”. Completion date of the verification analysis: 14 February 2020