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- МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ ПРОВЕДЕНИЯ ОЦЕНКИ ДОСТОВЕРНОСТИ НАУЧНЫХ ДАННЫХ С ПОМОЩЬЮ СИСТЕМЫ КЛАССИФИКАЦИИ, ОЦЕНКИ, РАЗРАБОТКИ И ЭКСПЕРТИЗЫ РЕКОМЕНДАЦИЙ GRADE
- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

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ANALYSIS OF COSTS OF MEDICINAL PRODUCT LANREOTIDE (SOMATULINE® AUTOGEL®) IN THE TREATMENT OF PNET DEGREE GRADE 1 OR 2 (WITH TUMOR PROLIFERATION INDEX [KI-67]<10%), IN ADULT PATIENTS WITH NON-FUNCTIONING NON-METASTATIC OR METASTATIC TUMORS

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Summary
Analysis of costs of using lanreotide in patients with GEP-NETs grade 1 or 2 originating from the pancreas(with tumor proliferation index of [Ki-67] <10%) was carried out in this study.
Targeted drugs with indications for treatment of pancreatic NETs in the Russian Federation were used for comparison: sunitinib and everolimus.
Pharmacoeconomic study was carried out using methods of «cost-effectiveness» analysis including a sensitivity analysis.
The study considered the direct costs which included the costs of treatment and the methods of diagnosis according guidelines of RUSSCO (MRI, biopsy and biochemistry blood analysis).
As a result, it was found that the average cost of main pharmacotherapy per patient annually using lanreotide is lower than the average cost of treatment using sunitinib or everolimus by 55.2% and 51.9% (845 000 roubles, 1,886,991 roubles and 1758 443 roubles), respectively.
This pharmacoeconomic analysis showed that the average total cost of the main drug treatment and medical care services in the treatment of pancreatic NETs using lanreotide is 886,036 roubles.
That is lower than the total cost of treatment using sunitinib (1,928,027 roubles) or everolimus (1,799,479 roubles) by 54.0% and 50.8%, respectively.
When analyzing the 'cost effectiveness', progression-free survival (PFS) was chosen as an efficiency criterion.
Considering the results of «cost - effectiveness» analysis, the use of lanreotide for the treatment of pancreatic NETs has a significant advantage over therapy using sunitinib or everolimus in terms of median progression-free survival (PFS), CER of lanreotide is lower than CERof sunitinib and CER of everolimus (73 836 rub/month, 160 660 rub/month and 149 957 rub/month respectively) i.e., lanreotide is the option in treatment. This study has limitations due to study design (lareotide open label study) and difference in population between lanreotide study and sunitinib and everolimus studies.

Keywords: *neuroendocrine tumors (NETs), pancreas, tumor proliferation index, lanreotide, sunitinib, everolimus, pharmacoeconomics, efficiency analysis, analysis of «cost-effectiveness»*

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) comprise a heterogeneous group of tumors originating from neuroendocrine cells of embryonic gut tube. These tumors often localize in the gastrointestinal tract (GI) tract and pancreas (P) [1]

Prevalence of NET in Europe in 2013 was 26.9 cases per 100 000. The prevalence of NETs originating from the gastrointestinal tract and pancreas was 20 cases per 100 000 [2], and the prevalence of NETs originating from the pancreas is 1.04 cases per 100 000 [2]..

This classification proposed to 3 groups of tumors – Grade 1, Grade 2, Grade 3[3].

Survival prognosis for patients with NET is very controversial and depends on the degree of tumor differentiation and tumor grade [1.11].

In 2010 World Health Organization (WHO) proposed a new classification for gastrointestinal and pancreatic NETs (Table 1). This classification proposed to divide tumors into 3 groups - Grade 1, Grade 2, Grade 3 [3]

Table 1. WHO 2010 classification of GEP NET

Grade 1	Well differentiated endocrine tumor
Grade 2	Well differentiated endocrine carcinoma
Grade 3	Poorly differentiated endocrine carcinoma
	Mixed exocrine-endocrine tumors
	Tumor-like lesions

European Neuroendocrine Tumors Society (ENETS) proposed to divide gastrointestinal and pancreatic NETs into 3 main groups according to the degree of malignancy. The degree of malignancy according to this classification is determined by tumor cell proliferation index Ki-67 (Table 2) [4].

Table 2. ENETS classification of GEP NET

Gradation	Ki-67 (%)
G1	≤ 2
G2	3-20
G3	> 20

Antigen Ki-67, which is the base for NET gradation, is a proliferation marker widely used in pathology practice. The expression of Ki-67 makes it possible to identify tumor cells that are in the active phase of the cell cycle. Actively proliferating tumor cells constitute a 'growth fraction' of neoplasm. Proliferative activity is a major factor both for the mechanism of malignant transformation of cells and for the biological behavior of the existing tumor. Proliferative activity can be considered one of the most important characteristics of the tumor phenotype, which largely determines the rate tumor growth, the risk of metastasis, the potential response to therapeutic measures and outcome. A large number of factors that influence the course and outcome of cancer diseases exert their pathogenic effect on the tumor via changes in proliferative activity [5,6].

Assessment of tumor cells proliferative activity is necessary not only to determine the biological characteristics of the tumor, but also for choosing the right therapy [6].

Index of proliferative activity is different in different tumors, being a prognostic indicator determining the clinical course and prognosis of the disease.

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Index of proliferative activity below 10% suggests that tumor can be considered less aggressive. Proliferative activity index above 20% suggests that tumor can be regarded a highly aggressive. High Ki-67 level suggests that a tumor is more likely to respond to chemotherapy, and low level index suggests that the tumor will respond better to hormone therapy [7,4].

This pharmacoeconomic study was conducted in order to analyze and select the most preferred drug for the treatment of GEP-NETs in patients with highly differentiated tumors (Ki <10%), i.e., less aggressive tumors that are subject to hormonal therapy.

Although it has not been evaluated in randomized trials, but it is assumed that surgical treatment for GEP-NET provides the best chance to prolong survival. The main objective of surgical treatment is a resection and removal of metastases [8,9,10]. However, a large number of patients suffer unresectable tumor. In these cases the main objective of therapy is to control the progression [11].

Only a few drugs for the treatment of advanced NET were registered based on their antiproliferative activity (effective inhibition of tumor growth). Available data suggest that the use of modern targeted therapies that selectively influence the relevant molecular targets can increase progression-free survival in patients with advanced metastatic pancreatic NETs. It should be noted that analogues of somatostatin characterized by a favorable safety profile and are widely used for the treatment of symptoms related to hormone hypersecretion [12,13,14].

There are only two targeted drugs in the Russian Federation with registered indications for the treatment NET originating from the pancreas: sunitinib and everolimus. The efficacy of these drugs has been confirmed in randomized phase III trials [15,16].

Lanreotide is a somatostatin analogue having an antiproliferative effect on NETs. Clinical studies have shown that lanreotide significantly increases progression-free survival in patients with metastatic gastrointestinal tract and pancreas NETs grade 1 or 2 (Ki-67 <10%). In December 2014 US Food and Drug Administration (FDA) approved lanreotide for treatment of patients with GEP-NETs [17,18], and at the end of 2015 the Ministry of Health of the Russian Federation approved this indication in Russia.

In connection with the foregoing, the aim of this study was to conduct a pharmacoeconomic analysis of the use of lanreotide for treatment of pancreatic NETs in patients with highly differentiated tumors (grade 1 or 2, Ki <10%) in the Russian Federation.

Materials and methods

Efficacy analysis is the first step of the 'cost-effectiveness' analysis conducted in this study. Efficacy analysis aims to find efficacy parameter that meets the objectives of the study, as well as to obtain data characterizing the analyzed technologies from the perspective of the selected efficacy parameter.

In this study, the efficacy analysis was carried out by analyzing the existing randomized clinical trials (RCTs) data, i.e. it has a retrospective design. Thus, data search was performed to obtain data regarding efficacy parameters of the analyzed technologies. Information search has been carried out primarily in specialized libraries and databases (DB). To find the relevant RCTs the following databases were used: Pubmed and Medlink.

Due to the fact that the treatment of NETs is a long-term process, the overall survival (OS) rates are commonly not achieved in relevant RCTs due to the limited duration of the study, so when studying this type of the disease the main criterion of efficiency is considered to be progression control, i.e., progression-free survival (PFS). That is why the rate of progression-free survival (PFS) was selected in the analysis of «cost-effectiveness» in this study as the criterion of effectiveness [21,22,23].

The next stage of this study was to conduct a cost-benefit analysis. Cost analysis aimed to assess the cost of comparable medical technologies.

This pharmacoeconomic study was conducted from the perspective of the health care system, considering direct medical costs (costs of diagnostic and therapeutic medical services), that required obtaining relevant data on the prices of medicinal products (drugs) and medical services.

Costs values of medicinal products were obtained from the state register of medicinal product manufacturer maximum sale prices, included in the list of vital and essential medicines (as of 16/12/2015).

Tariff agreement on health care payments provided by the territorial program of compulsory health insurance in Moscow in 2015 from 25.12.2014 (last revised at the time of the study) was used as a source of information on the cost of medical services.

Efficacy analysis

At this stage of the study, in order to obtain data on the efficacy of lanreotide, sunitinib and everolimus, a search for RCTs including adult patients with non-functioning non-metastatic or metastatic tumors, investigating the impact of the above drugs on patients with Grade 1 or 2 NETs (with an index of the proliferation of the tumor [Ki-67] <10 %) with pancreatic origin was conducted.

Pubmed and Medlink databases were used to search for relevant studies. The following key words were used for search: «metastatic», «enteropancreatic», «neuroendocrine tumors», «sunitinib», «everolimus», «lanreotide».

Three works were found during a searching for data on the efficacy of sunitinib in pancreatic NETs, two of which were excluded from the study. The first work was excluded due to the fact that sunitinib dosing system did not met currently recommended. Sunitinib was taken at a dose of 50 mg per day for 4 weeks followed by a two week drug-free period, whereas, the recommended dosage regimen is 37.5 mg per day for long-term, i.e. without interruption [4.25].

The second study was excluded due to the fact that only 12 patients were included in the study. And the third study was an RCT phase III study in which the effect of sunitinib has been investigated in 86 patients, so the preference was given to that RCT [15,26].

Three relevant studies were found providing data on the effectiveness of everolimus. And only one most appropriate study was selected for the pharmacoeconomic evaluation. One study was excluded due to the fact that the proportion of patients with NETs of pancreatic origin accounted only for 50%, and the rest of patients had NETs of other origin. The second work was a phase II trial, which investigated the efficacy and safety of the drug in China patients (overall 79 patients participated in the study, 44 of them received everolimus). Finalally, preference was given to the phase III trial, in view of the fact that it included a larger number of patients (207 receiving everolimus) [16,27,28].

During the analysis of lanreotide efficacy, we found only one RCT, providing data corresponding to previously selected trials, that allowed to include this work in our pharmacoeconomic analysis [18]. It should note that not all eligible core study patients continued to be followed into the open-lable study (OLE); OLE study was not specifically designed to measure efficacy; PFS estimates was done on locally rather than centrally assessed PD; post hoc sensitivity analysis that included all patients with SD in the core study who did not continue into the OLE study and designated them as having PD at the first OLE assessment.

Thus we selected three studies for efficacy analysis. Each trial was a Phase III RCT to prove a hypothesis that these medicinal products are able to prolong time to disease progression. The studies of sunitinib and everolimus included patients with progression disease (PD), patients with stable disease (SD) participated in the lanreotide study. At the same time, according to recent recommendations of ENETS, for antiproliferative purpose lanreotide may be used in stable or progressive disease[30]. Table 3 provides the data on the RCTs selected.

It should be noted that in the study lanreotide effect on tumor progression, median progression-free survival was (PFS) was not reached during the study period. It was achieved only during open-label extension being 29,7months. Efficacy analysis showed that the highest median of PFS was achieved in lanreotide group. Median PFS for this group of patients was 29,7months compared to 11,4 months and 11.0 months for patients treated with sunitinib and everolimus respectively.

Table 3. RCTs used in pharmacoeconomic analysis

Frist author, year	Tumor localization	Study drug	Number of patients	Efficacy criterion	Result, median (months)
Raymond[15], 2011	Pancreas	Sunitinib	86	PFS	11,4
Yao[16], 2011	Pancreas	Everolimus	207	PFS	11.0
Caplin[18], 2016	NET(pancreas data)	Lanreotide	33	PFS	29,7

*In the core study median PFS in pNET subgroup was not reached(vs placebo)

Cost analysis

Costs of NET pharmacotherapy using lanreotide, sunitinib and everolimus were calculated at this stage of the study. Course dose of the therapy was determined based on the dosing regimens, indicated in the corresponding prescribing information leaflets.

Costs values of medicinal products were obtained from the state register of medicinal product manufacturer maximum sale prices, included in the list of vital and essential medicines (as of 16/12/2015)[19].

It should be noted that data on lanreotide costs were provided by the Manufacturer. Pharmacoeconomic analysis was performed considering the cost of lanreotide (syringe 120 mg, N1) was 65 000 roubles.

Data on the costs of comparators are provided in Table 4.

Average cost of therapy for one patient using sunitinib during one-year period, provided the daily dose is 37.5 mg, was 1 886 991 roubles

$$\left(\frac{48\ 252\times365\times37,5}{12,5\times28}=1\ 886\ 991\,\text{rub}\right).$$

Similarly we calculated the cost of therapy for one patient using everolimus during one-year period, provided the daily dose is 10 mg: 1 758 443 roubles.

$$\left(\frac{144\ 530\times365\times10}{10\times30}=1\ 758\ 443\,\text{rub}\right)$$

Lanreotide therapy costs was calculated considering the dosing regimen of 120 mg once per 28 days. The number of treatment days per year was calculated dividing the duration of one treatment cycle by the number of day per year. $\left(\frac{28}{365}\approx 13\right)$.

Thus the cost of treatment for one patient using lanreotide was 845 000 roubles $\left(\frac{65\ 000\times120\times13}{120}=845\ 000\text{rub}\right)$

Graphical presentation of data obtained during cost analysis of the main pharmacotherapy of pancreatic NET is provided in Figure 8.

As we can see here, the cost of pharmacotherapy using lanreotide is lower than sunitinib or everolimus by 55.2% and 51.9% respectively.

Calculation of costs of medical care services in patients with pancreatic NET was also performed during cost-analysis. The list of necessary medical care services was used from practical guidelines for the medical treatment of patients with malignant neoplasms (RUSSCO)[4]. We did not consider radical surgical interventions among medical care services because of lack of intervention rate data. In addition to physician visits, necessary medical care services list included imaging methods (abdominal and pelvic MRI, etc.), biopsy and chemistry (chromogranin A determination, complete blood count, biochemical blood assay, etc.).

Tariff agreement on health care payments provided by the territorial program of compulsory health insurance in Moscow in 2015 from 12.25.2014 (last revised at the time of the study) was used as a source of information on the cost of medical services [20]. Data on the cost of serum chromogranin A and serotonin analyses were obtained from the internet source «invitro.ru», as these were not stated in the Tariff Agreement on health care payments provided by the territorial program of compulsory health insurance [24].

According to recommendations, there is a range of accounted medical care services, required for patients with pancreatic NET. These include examination and biochemistry analyses every 3 months, and also imaging methods once per 6 months [4]. Thus, medical care services for each patient are a constant value, identical for all the patients. The cost of medical care services for one patient with pancreatic NET per year is 41 036 roubles.

Table 4. Data on maximum sales price for comparators

№	INN	TN	Pharmaceutical form (PF)	Manufacturer	Amount of PF per peer package	Maximum sale price, excluding VAT
1	Sunitinib	Sutent®	Capsules 12.5 mg	Pfizer, Italy	28	48 252
2	Everolimus	Afinitor®	Tablets 10 mg	Novartis, Switzerland	30	144 530
3	Lanreotide	Somatuline® Autogel®	Syringe 120 mg	Ipsen, France	1	65 000

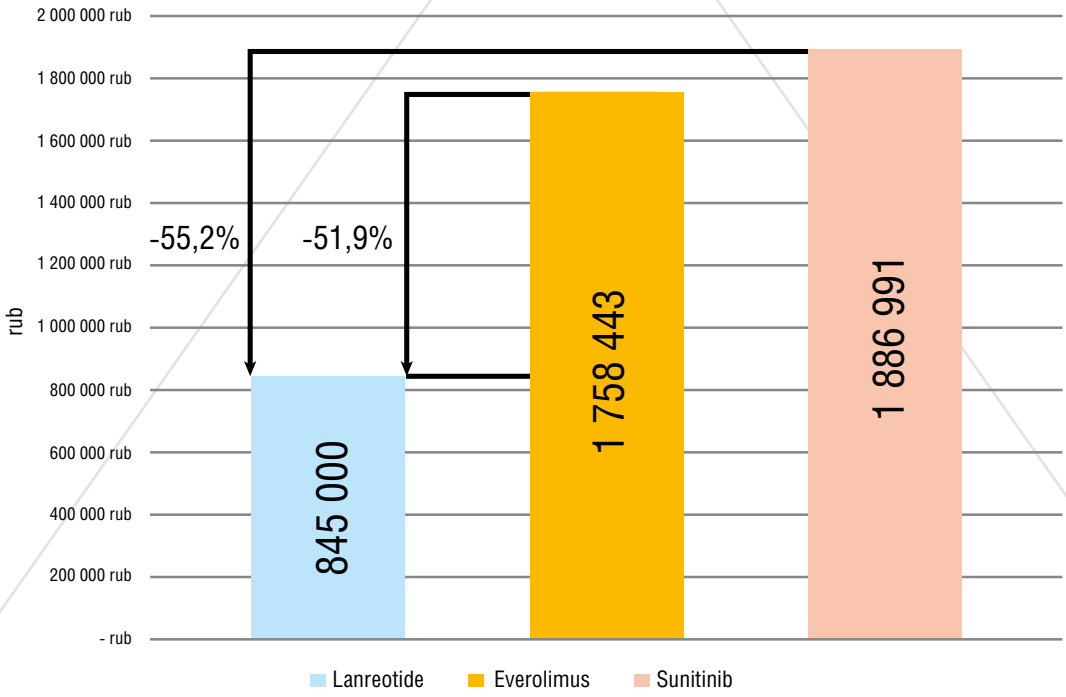

Figure 8. Costs of the main pharmacotherapy of pancreatic NETs (roubles)

Table 5. Data on the average costs of treating of one patient with pancreatic NET per year

Drug	Item of Cost	Costs (roubles)	Total costs (roubles)
Lanreotide	Main pharmacotherapy	845 000	886 036
	Medical care services	41 036	
Sunitinib	Main pharmacotherapy	1 886 991	1 928 027
	Medical care services	41 036	
Everolimus	Main pharmacotherapy	1 758 443	1 799 479
	Medical care services	41 036	

According to data presented in Table 5, the total costs of treatment courses with lanreotide, sunitinib and everolimus were 886,036 roubles., 1,928,027 roubles, and 1,799,479 roubles, respectively.

Cost-effectiveness analysis

Cost-effectiveness aims to make a complex evaluation of a medical technology in order to determine the most efficient expenditure of scarce health care resources.

The median progression-free survival (PFS) was used as a measure of efficacy. The coefficients of "cost-efficiency" were calculated using the following equation:

$$CER = \frac{Cost}{Ef}$$ where:

Cost - costs for the efficiency period

Ef - Median PFS (months).

CER – 'cost- effectiveness' coefficient according to PFS

Lanreotide CER (median PFS) = 2,192,939 roubles/29,7months = 73 836 roubles/month

Sunitinib CER (median PFS) = 1,831,626 roubles/11.4 months = 160 669 roubles/month

Everolimus CER (median PFS) = 1,649,523 roubles/11.0 months= 149 957 roubles/ month

'Cost- effectiveness' ratio according to progression-free survival (PFS) in the treatment of pancreatic NETs using lanreotide as a primary therapy was 73,836 roubles for one month progression-free survival, and using sunitinib and everolimus it was 160,669 and 149,957 , respectively.

According to the ratios of "cost-effectiveness" based on efficacy criterion - median progression-free survival (PFS), the coefficient of "cost-effectiveness" for lanreotide lower than the corresponding coefficients for sunitinib and everolimus. Based on these data we can conclude that lanreotide therapy requires the lowest cost to achieve the same unit of efficiency, and can be regarded as the main alternative.

Analysis of the "budget impact"

Due to the fact that the management of patients with pancreatic NET is not limited to the costs of drug therapy, there is a need to analyze "effect on the budget." This analysis compares the total cost of using two health care technologies. The analysis allows calculate the amount of money that can be saved, or vice versa, you need to spend extra for the use of certain healthcare technology.

Analysis of the "budget impact" was carried out expressing results in a relative value, using the following equation:

$$BIA = \frac{S(1)}{S(2)} - 1$$ Where:

BIA – result of the budget impact analysis;

S (1) - total economic impact of health technology 1;

S (2) - the total economic impact of health technology 2 [29].

Budget impact analysis in the case of using lanreotide showed that the total cost of treating a single patient with pancreatic NET (including medical care services) is lower by 54.0% and by 50.8% compared to sunitinib and everolimus, respectively.

Graphical presentation of data on the total cost of pancreatic NETs therapy using comparators is shown in Figure 9.

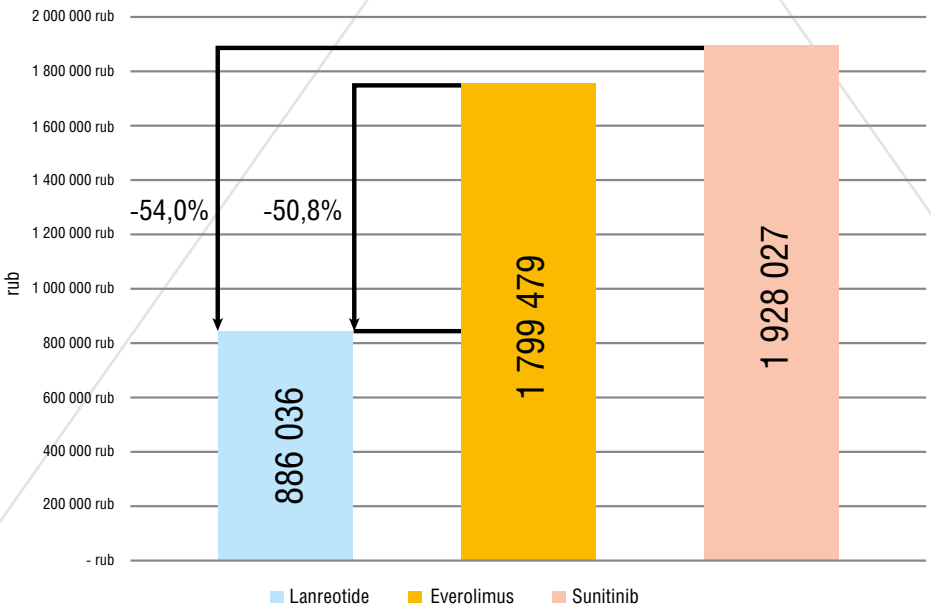

Figure 9. Total costs for pancreatic NET treatment (roubles)

Sensitivity Analysis

Univariate sensitivity analysis was performed to determine the robustness of the results obtained after the «cost-effectiveness» analysis.

Price change was regarded as an influencing factor.

To determine the stability of the results obtained, the price of lanreotide hypothetically changed by 50% in the direction of increasing and decreasing of its original value, analyzing the degree of change of relevant harmacoeconomic parameters (Table 6).

Table 6. Univariate analysis of sensitivity of pharmacoeconomic parameters depending on changes in the cost of medicinal product lanreotide

Parameters	Price of lanreotide % (abs)		
	- 50% (32 500 roubles)	Initial values (65 000 roubles)	+50% (97 500 roubles)
CER according to median PFS	38 628	74 997	109 045

After the 50% theoretical increase of the lanreotide price the «cost - effectiveness» ratio in terms of progression-free survival (PFS) amounted to 109,045. This parameter even after the 50% increase in price was lower than those of sunitinib and everolimus.

Sensitivity analysis showed that the drug therapy using lanreotide remains the predominant alternative according to the results obtained after analysis of «cost - effectiveness» in the setting of changing the price in the range of -50% to + 50%.

Conclusions

As a result of pharmacoeconomic analysis of lanreotide treatment for NETs Grade 1 or 2 (with tumor proliferation index of [Ki-67] <10%) having the pancreatic origin in adult patients with non-metastatic or metastatic non-functioning tumors it was found that:

- The costs for main pharmacotherapy using lanreotide costs are lower compared to sunitinib and everolimus by 55.2% and 51.9%, respectively;
- Budget impact analysis showed that the total cost of main pharmacotherapy and medical care services when treating pancreatic NETs using lanreotide are lower than total costs using sunitinib or everolimus by 54.0% and 50.8%, respectively;
- From the perspective of cost-effectiveness analysis the use of lanreotide for the treatment of pancreatic NETs has a significant advantage over drug therapy using sunitinib and everolimus in terms of median progression-free survival (PFS), i.e., it is main alternative;
- Sensitivity analysis demonstrated that lanreotide therapy remains the predominant alternative according to the results of cost-effectiveness analysis in the setting of changing the price in the range of -50% to + 50%.

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