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Research article

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Study of bioequivalence of veterinary drugs "Pinpramil" and "Milbemax" in dogs

ABSTRACT

The article presents the results of studying the bioequivalence of the reproduced drug "Pinpramil" in comparison with the reference drug "Milbemax". The experiments were conducted on 12 dogs, which were divided into two equal groups of 6 animals each. Dogs of one of the groups were given a reproduced drug, and animals of the other group were given a reference drug. The studied drugs were injected into the body of dogs once, individually, orally at a dose of the active substance, which corresponded to 0.5 mg of milbemycin oxime and 5 mg of praziquantel per 1 kg of body weight. After administration of the drugs, blood samples were taken from animals 14 times within 96 hours for subsequent production of serum, in which the content of praziquantel (including its active metabolite, trans-4-hydroxypraziquantel) and milbemycin oxime were determined by high-performance liquid chromatography. The obtained concentrations of these substances served as the basis for calculating their pharmacokinetic parameters in the body of dogs. The statistical analysis showed that the two-way confidence intervals for the Cmax, AUC0-t, AUC0-∞ ratios were in the range of 80–125%, and the Cmax/AUC0-t ratios were 75–133%. Thus, the research results have demonstrated that the drugs "Pinpramil" and "Milbemax" are bioequivalent.

Key words: bioequivalence, pharmacokinetics, milbemycin oxime, praziquantel, dogs, blood

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Научная статья

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Изучение биоэквивалентности ветеринарных препаратов «Пинпрамиль» и «Мильбемакс» в организме собак

РЕЗЮМЕ

В статье представлены результаты изучения биоэквивалентности воспроизведенного препарата «Пинпрамиль» в сравнении с референтным препаратом «Мильбемакс». Опыты были проведены на 12 собаках, которых разделили на две равные группы — по 6 животных. Собакам одной из групп задавали воспроизведенный препарат, животным другой группы — референтный. Изучаемые препараты вводили в организм собак однократно, индивидуально, пероральным путем в дозе по действующему веществу, которая соответствовала 0,5 мг мильбемицина оксима и 5 мг празиквантела на 1 кг массы тела. После введения препаратов у животных были отобраны пробы крови 14 раз в течение 96 часов для последующего получения сыворотки, в которой методом высокоэффективной жидкостной хроматографии определяли содержание празиквантела (в том числе его активного метаболита — транс-4-гидроксипразиквантела) и мильбемицина оксима. Полученные значения концентраций этих веществ послужили основой для расчета их фармакокинетических параметров в организме собак. Проведенный статистический анализ показал, что двусторонние доверительные интервалы для отношений C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ находились в пределах 80–125%, а отношений C_{max}/AUC_{0-t} — 75–133%. Таким образом, результаты исследований продемонстрировали, что препараты «Пинпрамиль» и «Мильбемакс» являются биоэквивалентными.

Ключевые слова: биоэквивалентность, фармакокинетика, мильбемицина оксим, празиквантел, собаки, кровь

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Introduction/Введение

Helminthiasis in carnivores is a disease caused by parasitic worms, or helminths. Both adult and young animals (puppies and kittens) can be affected by them. The large number of parasite eggs released into the environment by infected individuals can lead to infection even in pets that have never left the confines of an apartment, due to the introduction of pathogens into the home on clothing and shoes. Additionally, there is currently a popular trend of pet owners joining clubs (including dog clubs), which requires regular participation of dogs in exhibitions and competitions, involving the movement of animals within the country and abroad. In such conditions, owners are forced to implement a comprehensive set of preventive measures, including deworming [1–3].

The eradication of parasitic worms presents a complex challenge, as adult individuals and their larvae react differently to various antiparasitic agents. Anthelmintic drugs may contain a single active component intended to destroy a specific class of worms, or they may have a complex action on multiple parasite species by incorporating several active components [4, 5].

The aim of the conducted study was to investigate the bioequivalence of complex antiparasitic drugs, "Pinpramil" (manufacturer/developer: LLC "VIC — Animal Health," Russia) and "Milbemax" (manufacturer: Elanco France SAS, France). The drugs are available in the form of oral tablets, which contain milbemycin oxime and praziquantel as active ingredients.

Milbemycin oxime is a macrocyclic lactone obtained through the enzymatic activity of Streptomyces hygroscopicus var. Aureolacrimosus. It is active against nematode larvae and adults that parasitize the gastrointestinal tract of dogs, as well as against the larvae of Dirofilaria immitis. The mechanism of action of milbemycin is based on increasing the permeability of cell membranes to chloride ions (Cl), leading to hyperpolarization of nerve and muscle cell membranes, paralysis, and death of the parasite [6–8].

Praziquantel is an acylated derivative of pyrazin-isoquinoline and exhibits pronounced activity against cestodes and nematodes. By increasing the permeability of the parasite's cell membranes to calcium ions (Ca2+), it causes depolarization of the membranes, muscle contraction, and tegument destruction, leading to the death of the parasite and its elimination from the animal's body. Praziquantel is metabolized in the body to trans-4-hydroxypraziquantel.

The simultaneous use of two active ingredients with different spectra and mechanisms of antiparasitic action in one dosage form has allowed the creation of a universal complex drug that is prescribed to dogs for therapeutic and preventive purposes in cases of nematode and cestode infections, as well as mixed nematode-cestode infestations.

Bioequivalence studies allow for a relatively short-term assessment of the safety and efficacy of a new drug compared to a reference drug that has undergone a comprehensive set of clinical and preclinical studies. This enables the avoidance of prolonged and costly experiments on animals and facilitates the prompt introduction of a new drug to the veterinary market [9–12].

Table 1. **Body weight of dogs and doses of drugs received by them**
Таблица 1. **Масса тела собак и полученные ими дозы препаратов**

Animal No.	Gender	Body Weight, kg	Dose (of Milbemycin), mg per dog	Dose (of Praziquantel), mg per dog
		"Milbemax"		
1	Male	22,1	11,1	110,5
2	Female	21,5	10,8	107,5
3	Male	20,3	10,2	101,5
4	Male	20,1	10,1	100,5
5	Female	18,8	9,4	94,0
6	Male	21,6	10,8	108,0
		"Pinpramil"		
7	Female	22,3	11,2	111,5
8	Male	21,3	10,7	106,5
9	Male	19,0	9,5	95,0
10	Female	19,3	9,7	96,5
11	Male	22,4	11,2	112,0
12	Male	22,8	11,4	114,0

Materials and methods /
Материалы и методы исследования

The study described in the article was conducted in 2023. Two groups of mixed-breed dogs, aged 1–3 years and weighing 18.8–22.8 kg, were formed for the analog-based work. Each group consisted of 6 individuals. The dogs were housed in an animal shelter in the Moscow region.

A parallel study design was used for the experiments[1], which involved the simultaneous administration of the reproduced drug "Pinpramil" to one group of animals and the reference drug "Milbemax" to the dogs in the second group.

Before conducting the experiments, each animal was weighed to calculate the individual dose of the drug. The test drugs were administered to the dogs orally, individually, in a single dose. The dose of the drugs administered to each animal corresponded to 0.5 mg of milbemycin oxime and 5 mg of praziquantel per 1 kg of body weight.

In the experiment, tablets of "Pinpramil" and "Milbemax" were used, containing 12,5 mg of milbemycin oxime and 125 mg of praziquantel.

The individual body weight values of the experimental dogs and the corresponding doses of the active substances of the drugs are indicated in Table 1.

Blood samples were collected from dogs before the administration of the drugs (0 h) and at 15, 30, 45 minutes and 1, 2, 3, 4, 6, 9, 12, 24, 48, 72, 96 hours after drug administration. Blood samples were collected from 6 dogs in each group at each time point.

The blood was collected in disposable clot activator tubes. After clot formation and serum separation, the blood samples were centrifuged at 3500 rpm for 5 minutes. Subsequently, the serum was transferred to "Eppendorf" tubes in a volume of at least 1 ml, frozen, and transported in a frozen state in a thermos container to the "BIOVISOR" bioanalytical laboratory in Moscow (RUS).

During the study, the concentrations of active substances in the serum of dogs were determined. For this purpose, a validated method of quantitative determination of praziquantel, trans-4-hydroxypraziquantel, and milbemycin oxime in the serum samples was used, employing high-performance liquid chromatography with tandem mass spectrometric detection. The analysis was performed using a "Shimadzu LCMS-8050" chromatograph-mass spectrometer (Japan). The following parameters were considered during the validation of the method: linearity, extraction efficiency, specificity, precision, accuracy,

[1] Order of the Ministry of Agriculture of the Russian Federation dated March 6, 2018, No. 101 "On the Approval of Rules for Conducting Preclinical Studies of a Veterinary Medicinal Product, Clinical Studies of a Veterinary Medicinal Product, and Bioequivalence Studies of a Veterinary Medicinal Product."

limits of quantitative and qualitative determination, dilution acceptability, stability of the analyte and internal standard.

The obtained concentrations of praziquantel, trans-4-hydroxypraziquantel, and milbemycin oxime in the serum of dogs were used to calculate their pharmacokinetic parameters: the half-life of the active substance ($T_{1/2}$), the maximum concentration of the active substance (C_{max}), the area under the concentration-time curve from 0 to the last sampling time point (AUC_{0-t}), the area under the concentration-time curve from 0 to infinity ($AUC_{0-\infty}$), the mean residence time of the substance in the systemic circulation (MRT), and the ratio of AUC_{0-t} to $AUC_{0-\infty}$. The values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ served as the basis for evaluating the bioequivalence of the investigated drugs.

The data obtained during the study were statistically processed, which involved calculating the mean values, relative standard deviations from the means, and standard errors using "Microsoft Excel". The pharmacokinetic parameters were calculated using the PKSolver software (an add-in for Microsoft Excel, USA) with the application of a non-compartmental model for the distribution of the active substances of the drugs "Pinpramil" and "Milbemax" in the animal's body.

Results and discussion / Результаты и обсуждение

Based on the obtained data, it has been established that praziquantel is rapidly absorbed from the gastrointestinal tract, and it is detected in dog serum as early as 15 minutes after administration, both for the reproduced and reference formulations.

Fig. 1. Dynamics of changes in the concentration of praziquantel in the blood serum of dogs

Рис. 1. Динамика изменения концентрации празиквантела в сыворотке крови собак

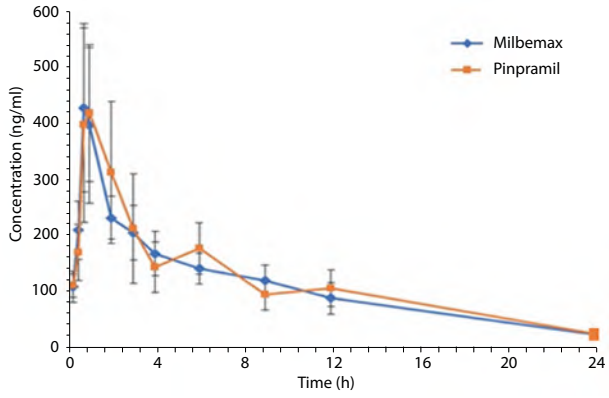

Fig. 2. Dynamics of changes in the concentration of trans-4-hydroxypraziquantel in the blood serum of dogs

Рис. 2. Динамика изменения концентрации транс-4-гидроксипразиквантела в сыворотке крови собак

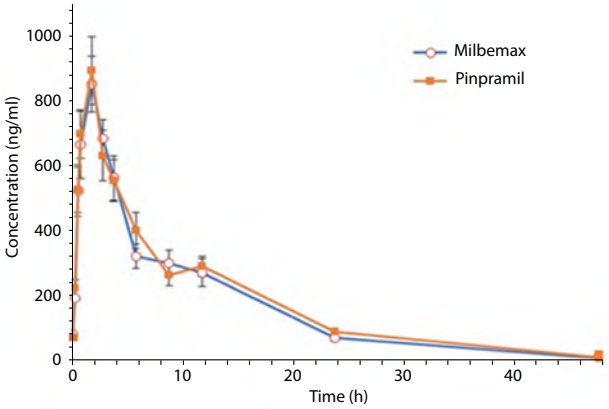

Table 2. **Pharmacokinetic parameters of praziquantel**

Таблица 2. **Фармакокинетические параметры празиквантела**

"Pinpramil"		
Parameter	**Mean value**	**RSD, %**
$T_{1/2}$, hour	6.79	20.4
C_{max}, ng/ml	531.54	14.4
AUC_{0-t}, ng/ml·h	2866.70	12.1
$AUC_{0-\infty}$, ng/ml·h	3122.17	13.5
$AUMC_{0-\infty}$, ng/ml·h	29 848.09	23.1
MRT, hour	9.47	11.0
$AUC_{0-t}/AUC_{0-\infty}$	0.92	2.9
"Milbemax"		
Parameter	**Mean value**	**RSD, %**
$T_{1/2}$, hour	6.45	14.4
C_{max}, ng/ml	466.74	21.3
AUC_{0-t}, ng/ml·h	2657.28	8.3
$AUC_{0-\infty}$, ng/ml·h	2885.36	5.4
$AUMC_{0-\infty}$, ng/ml·h	26 981.08	8.5
MRT, hour	9.39	11.7
$AUC_{0-t}/AUC_{0-\infty}$	0.92	3.0

For the reproduced formulation, "Pinpramil", the peak concentration of praziquantel in the blood was reached between 0.75 and 2 hours after administration, with a maximum level ranging from 413.32 to 607.26 ng/ml. Over the course of two days, the concentration of praziquantel in the serum gradually decreased and was below the limit of quantification of the method (5 ng/ml) after 48 hours.

A similar pattern was observed after administration of the reference formulation, "Milbemax": the concentration of praziquantel reached its maximum at 0.75 to 1 hour after administration and ranged from 359.18 to 594.31 ng/ml. Subsequently, its concentration in dog serum gradually decreased, and by 48 hours, it was also below the limit of quantification of the method (5 ng/ml)

The graph depicting the change in concentration of praziquantel in dog's blood is shown in Figure 1.

The obtained values of praziquantel concentration in the blood allowed for the calculation of its pharmacokinetic parameters, which are presented in Table 2.

B the course of the study, data were obtained indicating that praziquantel is rapidly metabolized to trans-4-hydroxypraziquantel, which is detected in the blood 15 minutes after administration of the drug.

For the reproduced "Pinpramyl" preparation, the maximum concentration of trans-4-hydroxypraziquantel in the blood was reached within 1–3 hours after administration of the drug, with the maximum level ranging from 725.56 to 1171.87 ng/ml. Subsequently, the analyte content decreased and by 72 hours did not exceed the lower limit of quantification of the method.

In the case of the reference drug "Milbemax", the level of trans-4-hydroxypraziquantel reached its maximum within 1–3 hours after administration of the drug and ranged from 707.31 to 1046.70 ng/ml. Subsequently, the concentration of the metabolite in the blood serum of dogs decreased and by 72 hours did not exceed the lower limit of quantification of the method.

The comparative graph depicting the changes in the level of trans-4-hydroxypraziquantel in the blood of dogs is shown in Figure 2.

Table 3. **Pharmacokinetic parameters of trans-4-hydroxypraziquantel**

Таблица 3. **Фармакокинетические параметры транс-4-гидроксипразиквантела**

"Pinpramil"		
Parameter	**Mean value**	**RSD, %**
$T_{1/2}$, hour	7.53	7.9
C_{max}, ng/ml	947.35	19.5
AUC_{0-t}, ng/ml·h	8703.71	8.0
$AUC_{0-\infty}$, ng/ml·h	8813.92	8.0
$AUMC_{0-\infty}$, ng/ml·h	97 749.74	11.3
MRT, hour	0.99	0.4
$AUC_{0-t}/AUC_{0-\infty}$	0.92	2.9
"Milbemax"		
Parameter	**Mean value**	**RSD, %**
$T_{1/2}$, hour	6.98	20.3
C_{max}, ng/ml	920.63	13.0
AUC_{0-t}, ng/ml·h	8004.16	10.9
$AUC_{0-\infty}$, ng/ml·h	8144.11	9.8
$AUMC_{0-\infty}$, ng/ml·h	84 299.86	20.2
MRT, hour	10.31	14.4
$AUC_{0-t}/AUC_{0-\infty}$	0.98	1.5

Based on the obtained values of trans-4-hydroxypraziquantel concentrations in the serum of dogs, its pharmacokinetic parameters were calculated and are presented in Table 3.

Pharmacokinetics of milbemycin oxime in the serum of dogs

The obtained data indicate that milbemycin oxime is rapidly absorbed from the gastrointestinal tract and can be detected in the serum of dogs as early as 0.25 hours after a single administration of the studied drugs.

For the reproduced "Pinpramil" formulation, the maximum concentration of milbemycin oxime in the blood was reached within 1–4 hours after oral administration, with the maximum level ranging from 146.95 to 200.10 ng/ml. Subsequently, the concentration of this analyte in the serum decreased but remained above the lower limit of quantification of the method (> 3 ng/ml) even after 96 hours (4.098–9.583 ng/ml).

A similar pattern was observed after administration of the reference product "Milbemax": the concentration of milbemycin oxime reached its peak at 1–4 hours after administration and ranged from 144.498 to 230.568 ng/ml. The level of this substance then decreased, and at 96 hours, it ranged from 5.299 to 11.381 ng/ml.

The comparative graph depicting the changes in the concentration of milbemycin oxime in the blood of dogs is presented in Figure 3.

Fig. 3. Dynamics of changes in the concentration of milbemycin oxime in the blood serum of dogs

Рис. 3. Динамика изменения концентрации мильбемицина оксима в сыворотке крови собак

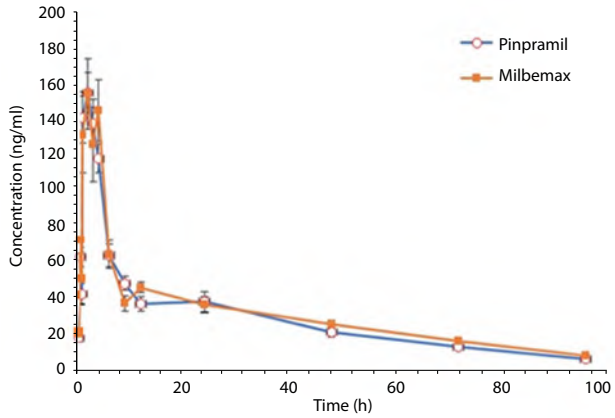

Table 4. **Pharmacokinetic parameters of milbemycin oxime**

Таблица 4. **Фармакокинетические параметры мильбемицина оксима**

"Pinpramil"		
Parameter	**Mean value**	**RSD, %**
$T_{1/2}$, hour	29.59	32.2
C_{max}, ng/ml	177.671	13.1
AUC_{0-t}, ng/ml·h	2651.35	15.0
$AUC_{0-\infty}$, ng/ml·h	2920.80	15.8
$AUMC_{0-\infty}$, ng/ml·h	113 728.38	27.1
MRT, hour	38.52	14.2
$AUC_{0-t}/AUC_{0-\infty}$	0,91	4,2
"Milbemax"		
Parameter	**Mean value**	**RSD, %**
$T_{1/2}$, hour	30.30	18.5
C_{max}, ng/ml	186.72	16.8
AUC_{0-t}, ng/ml·h	3004.98	12.8
$AUC_{0-\infty}$, ng/ml·h	3374.82	13.2
$AUMC_{0-\infty}$, ng/ml·h	143 263.39	22.3
MRT, hour	42.18	13.5
$AUC_{0-t}/AUC_{0-\infty}$	0.89	4.2

The pharmacokinetic parameters of milbemycin oxime, which were calculated based on the obtained values of its concentrations in the serum of dogs, are presented in Table 4.

The presence/absence of bioequivalence between the reproduced "Pinpramil" formulation and the reference product "Milbemax" (selected for studies based on similar pharmaceutical form and active substance content) was assessed in accordance with the Rules for Conducting Bioequivalence Studies of Medicinal Products of the Eurasian Economic Union (Decision No. 85 of the Eurasian Economic Commission). The bioequivalence of the products was evaluated based on the assumption of lognormal distribution of the measured parameters C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and $C_{max}/AUC_{(0-t)}$.

The results of calculating the confidence intervals for the ratios of pharmacokinetic parameters of the active substances in the "Pinpramil" and "Milbemax" formulations are presented in Tables 5–7.

Table 5. **Comparison of pharmacokinetic parameters of praziquantel after the use of "Milbemax (M)" and "Pinpramil (P)"**

Таблица 5. **Сравнение фармакокинетических параметров празиквантела после применения препаратов «Мильбемакс (М)» и «Пинпрамиль (П)»**

Confidence interval for the ratios of pharmacokinetic parameters of the "Pinpramil"/"Milbemax" drugs					
The ratio of:	**Mean value**	**min**	**max**	**min, %**	**max, %**
$C_{max}(P)/C_{max}(M)$	1.150	0.948	1.396	82.4	121.4
$AUC_{0-t}(P)/AUC_{0-t}(M)$	1.076	0.967	1.196	89.9	111.2
$AUC_{0-\infty}(P)/AUC_{0-\infty}(M)$	1.075	0.967	1.195	90.0	111.2
$C_{max}/AUC_{0-t}(P)/C_{max}/AUC_{0-t}(M)$	1.070	0.881	1.299	82.4	121.4

Table 6. **Comparison of pharmacokinetic parameters of trans-4-hydroxypraziquantel after the use of "Milbemax (M)" and "Pinpramil (P)"**

Таблица 6. **Сравнение фармакокинетических параметров транс-4-гидроксипразиквантела после применения препаратов «Мильбемакс (М)» и «Пинпрамиль (П)»**

Confidence interval for the ratios of pharmacokinetic parameters of the "Pinpramil"/"Milbemax" drugs					
The ratio of:	**Mean value**	**min**	**max**	**min, %**	**max, %**
C_{max}(P)/C_{max}(M)	1.020	0.853	1.220	83.6	119.6
AUC_{0-t}(P)/AUC_{0-t}(M)	1.090	0.987	1.204	90.5	110.5
$AUC_{0-\infty}$(P)/$AUC_{0-\infty}$(M)	1.084	0.988	1.189	91.1	109.7
C_{max}/AUC_{0-t}(P)/C_{max}/AUC_{0-t}(M)	0.936	0.785	1.117	83.8	119.3

Table 7. **Comparison of pharmacokinetic parameters of milbemycin oxime after the use of "Milbemax (M)" and "Pinpramil (P)"**

Таблица 7. **Сравнение фармакокинетических параметров мильбемицина оксима после применения препаратов «Мильбемакс (М)» и «Пинпрамиль (П)»**

Confidence interval for the ratios of pharmacokinetic parameters of the "Pinpramil"/"Milbemax" drugs					
The ratio of:	**Mean value**	**min**	**max**	**min, %**	**max, %**
C_{max}(P)/C_{max}(M)	0.956	0.815	1.121	85.2	117.3
AUC_{0-t}(P)/AUC_{0-t}(M)	0.881	0.757	1.024	86.0	116.3
$AUC_{0-\infty}$(P)/$AUC_{0-\infty}$(M)	0.864	0.738	1.010	85.5	117.0
C_{max}/AUC_{0-t}(P)/C_{max}/AUC_{0-t}(M)	1.085	0.939	1.253	86.6	115.5

For praziquantel, trans-4-hydroxypraziquantel, and milbemycin oxime, the two-sided confidence intervals for the ratios of Cmax, AUC_{0-t}, and $AUC_{0-\infty}$ were within the range of 80–125%, and the ratio of C_{max}/AUC_{0-t} was within the range of 75–133%. Thus, the conducted study demonstrated that "Milbemax" and "Pinpramyl" products are bioequivalent.

Conclusion/ Выводы

The results of the study on the comparative pharmacokinetics of the reproduced "Pinpramyl" drug and the reference "Milbemax" drug in dogs demonstrated that they are pharmaceutically equivalent. This was evidenced by the two-sided confidence intervals for the ratios of Cmax, AUC0-t, and AUC0-∞ being within the range of 80–125%, and the ratio of Cmax/AUC0-t being within the range of 75–133%.

Summarizing the conducted scientific research, it can be concluded that the biopharmaceutical properties of the "Pinpramyl" drug are comparable to the similar properties of "Milbemax", which was previously registered in the Russian Federation based on the results of preclinical and clinical studies confirming its quality, efficacy, and safety. Thus, the obtained results indicate that the domestically developed "Pinpramyl" drug, created within the framework of import substitution, possesses safety and therapeutic effectiveness similar to the reference drug. This allows recommending it for the treatment and prevention of helminth infections in dogs.

All authors bear responsibility for the work and presented data.

All authors made an equal contribution to the work.
The authors were equally involved in writing the manuscript and bear the equal responsibility for plagiarism.
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