PRUMA

HV HOSPITAL VETERINÁRIO

EVZ ESCOLA DE VETERINÁRIA E ZOOTECNIA

FF FACULDADE DE FARMÁCIA

UFG UNIVERSIDADE FEDERAL DE GOIÁS

Safe use of medicinal products in the veterinary medical field

PHENOBARBITAL

for dogs and cats with epileptic seizures

MAY 2023
VOLUME 1
NUMBER 1
ISBN : 978-65-00-66929-9

ISBN : 978-65-00-66929-9 VOLUME 1 I NUMBER 1 MAY 2023

Dados Internacionais de Catalogação na Publicação (CIP)
GPT/BC/UFG

U58 Universidade Federal de Goiás.
Informative report Phenobarbital for dogs and cats with epileptic seizures : safe use of medicinal products in the veterinary medical field. [electronic resource]. / Universidade Federal de Goiás; Members coordination Angela Ferreira Lopes, Bruno Benetti Junta Torres, Nathalie de Lourdes Souza Dewulf. - v. 1, n.1 (2023) – Eletronic data - Goiânia : Universidade Federal de Goiás , 2023.
il.

Required System: Adobe Acrobat Reader
Access mode: World Wide Web:
Any part of this publication may be reproduced, provided that the source. Also available in: farmarcia.ufg.br ; evz.ufg.br ; hospitalveterinario.evz.ufg.br
ISBN : 978-65-00-37835-1

1. Pharmacology . 2. Domestic animals – Epilepsy . 3. Phenobarbital. I. Lopes, Angela Ferreira. II. Torres, Bruno Benetti Junta. III . Dewulf, Nathalie de Lourdes Souza. IV. Universidade Federal de Goiás, Faculdade de Farmácia. V. Universidade Federal de Goiás, Escola de Veterinária.

CDU: 636.045:615

Bibliotecária responsável: Joseane Pereira / CRB1: 2749

ISBN : 978-65-00-66929-9 VOLUME 1 I NUMBER 1 MAY 2023

Informative report
Phenobarbital for dogs and cats with epileptic seizures

ISBN: 978-65-00-37835-1

*The figures used are multimedia elements provided by Canva, allowed for non-profit use.

Members
Coordination:
• Angela Ferreira Lopes (angela_lopes@ufg.br)
• Bruno Benetti Junta Torres (brunobjtorres@ufg.br)
• Nathalie de Lourdes Souza Dewulf (nlsdewulf@ufg.br)

Members Coordination:
•Amanda Alves Ferreira (Amandaalves2@discente.ufg.br)
•Amanda Cecília Teodoro Landim (amanda_landim@discente.ufg.br)
• Angela Ferreira Lopes (angela_lopes@ufg.br)
• Ariel Silvestre Freitas (arielsilvestre@discente.ufg.br)
• Brenda Garcia Bentivoglio da Silva (brenda_garcia@discente.ufg.br)
• Bruno Benetti Junta Torres (brunobjtorres@ufg.br)
• Ítala Letícia Meneses Santos (italameneses@discente.ufg.br)
• Julia Botelho Alcântara (juhbotelho.contato@gmail.com)
• Laura Carvalho Silva Pureza (laura.pureza@discente.ufg.br)
• Luana de Sousa Ribeiro (luanadsribeiro@discente.ufg.br)
• Luísa Moreira Costa Chagas (luisamoreira@discente.ufg.br)
• Nathalie de Lourdes Souza Dewulf (nlsdewulf@ufg.br)
•Nathânia Rodrigues Santiago (nathsantiago2@gmail.com)
• Thayron Rhangell Lima dos Santos (trhangell@discente.ufg.br)

Editorial design:
• Laura Carvalho Silva Pureza (laura.pureza@discente.ufg.br)

PRUMA HV EVZ FF UFG

ISBN : 978-65-00-66929-9 VOLUME 1 I NUMBER 1 MAY 2023

INDICATIONS

Phenobarbital is an effective, low-cost and safe antiepileptic drug (AED), so monitoring its use is necessary. Phenobarbital is the AED chosen as the first choice for most dogs and cats diagnosed with idiopathic epilepsy, i.e., the cause of which is of genetic origin, genetic suspicion or unknown[1]. In these patients, phenobarbital was shown to be effective in 60-93% of canines and 50-80% of felines[2,3].

Phenobarbital is also indicated in the treatment of structural epilepsy and reactive (provoked) seizures, in which recurrent epileptic seizures are secondary to intracranial diseases and extracranial disorders (toxic or metabolic), respectively 2,4. In these cases, in addition to phenobarbital treatment, the primary causes of epileptic seizures should be identified and treated.

ISBN : 978-65-00-66929-9 VOLUME 1 | NUMBER 1 MAY 2023

THERAPEUTIC GOALS

Checklist

Primary objective

- Eliminate epileptic seizures;

Secondary objectives

- Decrease frequency of seizures in at least 50% of episodes after initiation of phenobarbital therapy[4];
- Decrease the severity and duration of episodes and comorbidities associated with epilepsy, and avoid the adverse effects of phenobarbital as much as possible, improving patients' quality of life and their families.

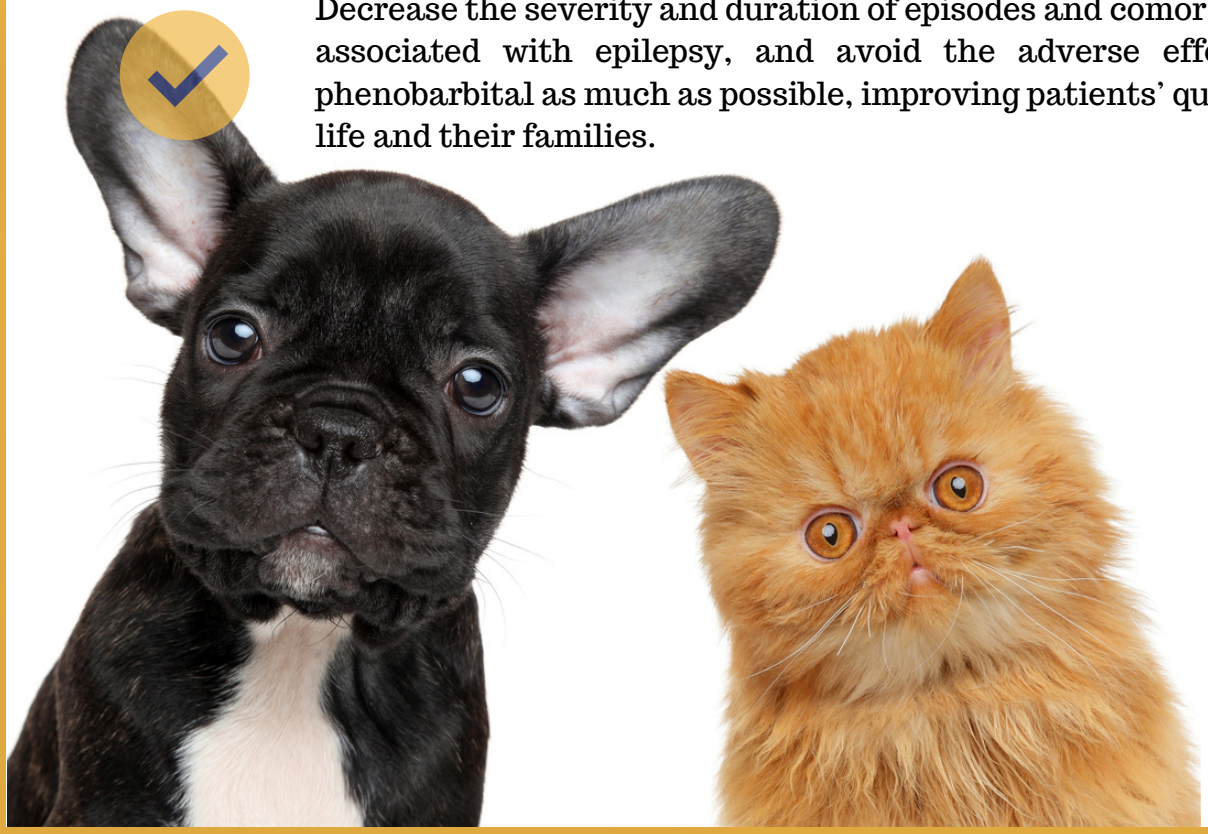

Table 1 - Dose, dosage, pharmaceutical form and monitoring of antiepileptic therapy with phenobarbital in dogs or cats.

THERAPY GOAL	DOSE	FREQUENCY	ROUTE OF ADMINISTRATION	PHARMACEUTICAL FORM	SPECIES	OBSERVATION
[a]Maintenance	3-5 mg/kg	Every 12h	Oral	Tablet, oral solution	Canine, feline	Seizure control appears to be better with the use of tablets.
	9 mg/kg	Every 12h	Topical	Transdermal gel	Feline	Application in the inner part of the ear pinna.
[b]Emergency	16-24 mg/kg	Total dose divided into 3-4 *bolus* smaller.	Intravenous	Solution for injection	Canine, feline	Monitor: potential risk of hypotension, mainly, in concomitant use of benzodiazepines.

[a]Maintenance: 3mg/kg dogs and cats with low frequency of seizures, i.e. no history of clustered crises (cluster) or sustained (status epilepticus); 5mg/kg patients with high frequency or a history of cluster, status epilepticus5. Specific cases of more difficult control can benefit from [5]administration every 8 hours 6. Half-life of 48 to 72 hours in monotherapy or in associated use.
[b]Loading dose: applied in emergency cases (cluster or status epilepticus) to control crises and achieve seric stabilization of phenobarbital.

Table 2 - Technical aspects related to the preparation and administration of antiepileptic therapy with phenobarbital in dogs or cats.

MEDICINE PHARMACEUTICAL PRESENTATION	ROUTES OF ADMINISTRATION		STABILITY	INCOMPATIBILITY
	IM	IV DIRECT		
Sodium phenobarbital, 100mg/ml, solution for injection, 2ml Ready to use	YES	Made in Bolus	Immediate use	Do not associate with other medicines in the same syringe or solution. Do not use IM medicine via IV - Risk of phlebitis

IM: Intramuscular
IV: Intravenosa

ISBN : 978-65-00-66929-9 VOLUME 1 | NUMBER 1 MAY 2023

Table 3 - Therapeutic monitoring of seric phenobarbital levels.

HOW TO PERFORM THE SERIC CONCENTRATION	Puncture a vein and place the blood in a dry tube, without serum separator, with a red or white cap. The animal must be fasting, and harvesting can be done immediately before administration of the medicinal product.
WHAT WOULD BE STABLE SERIC CONCENTRATION?	15 a 40 µg/mL of seric The recommended value for obtaining the best control of the frequency of seizures with minor adverse effects, regardless of pharmaceutical presentation or dose.
WHEN TO MEASURE?	At least 14 days after initiation of treatment. At least 14 days after dose adjustment Every 3 to 6 months, during treatment

Table 4 – Presentation and pharmaceutical form of phenobarbital with their respective concentrations and units available in the Brazilian market.

DRUG MANUFACTURER	CLASSIFICATION OF THE COMMERCIAL DRUG PRODUCT	HUMAN OR ANIMAL USE	PHARMACEUTICAL FORM	CONCENTRATION UNITS
GARDENAL® Sanofi Aventis	Reference Drug	Human use	Pill	50 mg Box with 20 pills 100mg Box with 20 pills
			Oral solution	40 mg/mL 20 mL bottle
FENOBARBITAL União Química	Generic Drug	Human use	Pill	100mg Box with 30 pills
			Oral solution	40 mg/ml 20 mL bottle
CARBITAL® Teuto	Similar Drug	Human use	Pill	100mg Box with 20 pills
			Solution for injection	200 mg/mL 1 mL ampoule
FENOCRIS® Cristália	Similar Drug	Human use	Solution for injection	100 mg/mL 2 mL ampoule
			Oral solution	40 mg/mL 20 mL bottle

PHARMACOTECHNICAL ASPECTS OF THE PREPARATION

- **PILLS**

They are used as adjuvants in the manipulation of compressed phenobarbital, corn starch, monohydrate lactose, povidone k30, magnesium stearate, calcium carbonate and dextrin. In this pharmaceutical form the drug can be manipulated or found commercially as a reference, generic or similar, as described in the table 5.

- **LIQUID FORMULATIONS**

Glycerol, 96°GL ethyl alcohol, new coccine dye, sodium saccharin dihydrate, sodium hydroxide, propylene glycol, raspberry essence and purified water can be found. Phenobarbital in liquid form is found in its industrialized form of reference and generic, as described in the table 5.

- **TRANSDERMAL FORMULATIONS**

They can be prepared in a polymer gel or composition base that increases absorption through the skin when applied to the ears of cats. The organogel Pluronic Lecithin Organogel (PLO) is the best basis for the formulation of transdermal phenobarbital, according to Delamaide Gasper et al. (2015). In Brazil, this gel-like medicine is only found in the manipulated form of.

* Information based on the package leaflet of the phenobarbital[15] medicine 15.

Table 6 - Adverse Reactions related to the use of phenobarbital

FREQUENT		
ADR	**DURATION**	**HANDLING**
Sedation and ataxia	Up to two weeks after the start or dose increase.	Case of deep sedation may be necessary to reduce the dose made under the guidance of the veterinarian.
Polyuria and polydipsia Polyphagia	While treatment lasts.	Increase the water access of the animal to prevent dehydration. Control the diet to prevent weight gain.
LESS FREQUENT		
ADR	**MONITORING**	
[a] Thyroid changes	Serum concentrations of thyroid hormones triiodothyronine (T_3T), tetraiodothyronine (T_4T), free tetraiodothyronine (T_4L) and canine thyroid stimulating hormone (TSHc).	
[a] Hepatotoxicity	Serum biochemistry (ALT, AST, AP, GGT, total bilirubins and fractions, total proteins, albumin, globulins, urea) and hepatic ultrasound.	
Blood dyscrasia (anemia, thrombocytopenia or pancytopenia)	Blood count.	
Superficial necrolytic dermatitis	Skin histopathology.	

[a]Every 6 months, monitoring should be carried out
ADR: Adverse Drug Reactions
AST: Aspartate aminotransferase
ALT: Alanine aminotransferase
GGT: Gama GlutamylTransferase
AP: Alkaline Phosphatase

Table 6 - Weaning from phenobarbital.

HOW TO PERFORM WEANING?	Phenobarbital should NOT be withdrawn abruptly, due to the risk of epileptic seizures associated with discontinuation (rebound effect).
	Reduce 20% of the indicated dose per month, withdrawn in 5 months. Reduce 25% of the indicated dose per month, withdrawn in 4 months. Ex.: patient received 100mg every 12h - 25% reduction at the same time: reduce to 75mg every 12h in the 1st month: reduce to 50mg every 12h in the 2nd month; reduce to 25mg every 12h no 3nd month; withdraw completely in the 4th month.
	If an abrupt interruption is required, it is recommended that another AED be added with an OVERLOAD DOSE before the outage. Recommended AED: Potassium bromide or levetiracetam.

AED - Antiepileptic drug.

ISBN : 978-65-00-66929-9 VOLUME 1 I NUMBER 1 MAY 2023

PHENOBARBITAL MECHANISM OF ACTION

Phenobarbital increases the epileptogenic threshold and acts to reduce the spread of the discharge of neurons around it by potentiating the inhibitory neurotransmitter GABA (Figure 1). Barbiturates generally act in increasing the time that chloride ion channels remain open, leading to hyperpolarization of the neuron and effectively reducing the dissociation rate of GABA and its .[23]

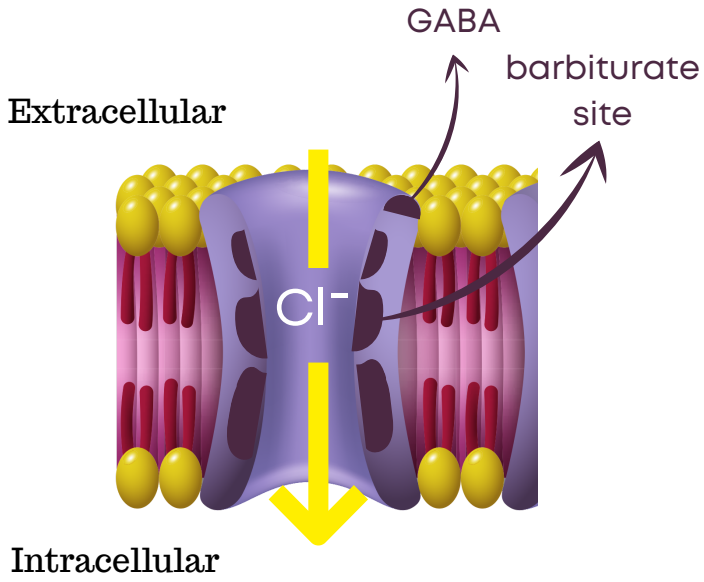

Figure 1. GABAergic receptor.
Source: author himself with elements provided on the Canva platfor

Because it is a liposoluble drug, it can be disseminated throughout the animal's organism, crossing the blood brain barrier and reaching brain tissue.

ISNN: VOLUME 1 I NUMBER 1 MAY 2023

CLINICAL CASE

A canine, two-year-old Labrador Retriever patient weighing 35kg was treated after having two epileptic seizures in the last six months. In neurological evaluation and complementary tests recommended by the International Veterinary Epilepsy Task Force (abbreviation in English, IVETF)[2] . no alterations were observed and was therefore diagnosed with idiopathic epilepsy. Treatment with one 100mg phenobarbital tablet (approximately 3mg/kg) was started every 12 hours. Two days after starting treatment, the tutor reported that the dog was very sleepy and asked if it could decrease the dose. It was explained that this adverse effect is expected and transient, so that the dose should not be decreased. After 14 days, the patient returned to collect a blood sample for the measurement of phenobarbital. On this occasion, the tutor reported that after seven days of administration, the dog no longer showed signs of drowsiness. Since the seeric measurement resulted in 27µg/mL of blood (reference 15-40 µg/mL) and the patient had no more seizures, we chose to increase the follow-up intervals. In one of its future returns, an increase in liver enzymes was observed, which caused the tutor to question the maintenance of the drug. It was explained that this change is expected due to the mechanism of action of the drug. In addition, as the dog had been without crises for more than a year, the tutor asked if it would not be possible to withdraw the medicine. He was then instructed on the possibility of attempted weaning and clinical observation, but that he should be aware that the crises could return. With the tutor's consent, a reduction of 25% of the initial dose was initiated, i.e., one and a half tablet (75mg) of phenobarbital was administered every 12 hours. The following week, the patient presented a new crisis and, therefore, the previous dose was reestablished and the tutor was instructed on the need to maintain the drug under constant supervision for the rest of his life. The patient did not have any more seizures, and we chose to increase the follow-up intervals.

EXAMPLES OF MEDICATION ERRORS INVOLVING THE USE OF PHENOBARBITAL	CHARACTERISATION OF PROBLEMS AND ASSOCIATED RISKS	RECOMMENDED SECURITY PRACTICES
Use every 24 hours	Difficulty IN MAINTAINING the seric stabilization and consequently, the control os the frequency of epileptic seizures	Administer the dose every 12h.
Delay in the time of administration of the drug.		Follow restrict information of time of administred
Decrease in dose by tutor due to drowsiness.	Difficulty in ACHIEVING seeric stabilization and, consequently, controlling the frequency of epileptic seizures.	Follow the recommendations veterinarian
Abrupt withdrawal of the drug by the tutor when seizures are controlled.	Recurrence of epileptic seizures	Follow the guidance of the veterinarian for maintenance or weaning, when recommended.
Not measurement of seric phenobarbital levels.	Low levels could lead the ineffective therapy	Periodic measurement of seric levels.
Withdrawal level drug due to increased liver enzymes	Worsening of the patient's clinical condition by difficulty in controlling recurrent epileptic seizures.	Maintenance of the drug with periodic clinical follow-up. Induction of liver enzymes is expected without hepatic impairment.
Abrupt withdrawal	Epileptic rebound seizures, usually more severe.	Weaning, when recommended: reduce the dose by 20-25% per month, until complete withdrawal.
Use of the drug without investigating the cause of epileptic seizures.	Difficulty in crisis control in cases where a underlying disease has not been identified and properly treated.	Clinical-neurological evaluation and complementary tests for the correct diagnosis.

ISBN : 978-65-00-66929-9 VOLUME 1 I NUMBER 1 MAY 2023

[1]. Charalambous M, Shivapour SK, Brodbelt DC, Volk HA. Antiepileptic drugs' tolerability and safety – a systematic review and meta-analysis of adverse effects in dogs. BMC Veterinary Research. [Online] 2016. [Quoted in : 28/10/2021] .12(1). Available in: doi:10.1186/s12917-016-0703-y

[2]. De Risio L, Bhatti S, Muñana K, Penderis J, Stein V, Tipold A, et al. International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. BMC Veterinary Research. [Online] 2015. [Quoted in : 28/10/2021]. 11(1). Available in: doi:10.1186/s12917-015-0462-1

[3]. Pakozdy A, Sarchahi AA, Leschnik M, Tichy AG, Halasz P, Thalhammer JG. Treatment and long-term follow-up of cats with suspected primary epilepsy. Journal of Feline Medicine and Surgery. [Online] 2013. [Quoted in : 28/10/2021]. 15(4): 267–273. Available in: doi:10.1177/1098612X12464627

[4]. Potschka H, Fischer A, Löscher W, Patterson N, Bhatti S, Berendt M, et al. International veterinary epilepsy task force consensus proposal: outcome of therapeutic interventions in canine and feline epilepsy. BMC Veterinary Research. [Online] 2015. [Quoted in : 28/10/2021]. 11(1). Available in: doi:10.1186/s12917-015-0465-y

[5]. Podell M. Manual of Canine and Feline Neurology. 4th ed. Platt SR, Olby NJ (eds.) Gloucester: BSAVA; 2014.

[6]. Stabile F, Barnett CR, De Risio L. Phenobarbital administration every eight hours: improvement of seizure management in idiopathic epileptic dogs with decreased phenobarbital elimination half-life. Veterinary Record. [Online] 2017. [Quoted in : 28/10/2021]. 180(7): 178–178. Available in: doi:10.1136/vr.104051

[7]. Yska JP, Essink GWG, Van Sorge AA, Bosch FH, Lankhaar G. Oral bioavailability of phenobarbital: a comparison of a solution in Myvacet 9-08, a suspension, and a tablet. Pharmacy World and Science. [Online] 2000. [Quoted in : 28/10/2021]. 22(2): 67–71. Available in: doi:10.1023/a:1008770519585

[8] Finnerty KE, Barnes Heller HL, Mercier MN, Giovanella CJ, Lau VW, Rylander H. Evaluation of therapeutic phenobarbital concentrations and application of a classification system for seizures in cats: 30 cases (2004-2013). Journal of the American Veterinary Medical Association. [Online] 2014. [Quoted in : 28/10/2021]. 244(2): 195–199. Available in: doi:10.2460/javma.244.2.195

[9] Gieger TL, Hosgood G, Taboada J, Wolfsheimer KJ, Mueller PB. Thyroid function and seric hepatic enzyme activity in dogs after phenobarbital administration. Journal of Veterinary Internal Medicine. [Online] 2000. [Quoted in : 28/10/2021]. 14(3): 277–281. Available in: doi:2.3.co;2">10.1892/0891-6640(2000)014<0277:tfashe>2.3.co;2

ISBN : 978-65-00-66929-9 VOLUME 1 | NUMBER 1 MAY 2023

[10] Reis BCM, Almeida JV, Melo VV. *Guia de Estabilidade de Medicamentos Injetáveis*. [Online]. 2ed. [Quoted in : 28/10/2021]. Available in: https://files.cercomp.ufg.br/weby/up/734/o/Tabela_de_estabilidade_de_medicamentos_injetaveis_2013.pdf?1409055816

[11] Riviere JE, Papich MG. *Veterinary pharmacology and therapeutics*. [Online] John Wiley & Sons; 2018. [Quoted in : 28/10/2021]. Available in: https://onlinelibrary.wiley.com/journal/13652885

[12]. Delamaide Gasper JA, Barnes Heller HL, Robertson M, Trepanier LA. Therapeutic serum phenobarbital concentrations obtained using chronic transdermal administration of phenobarbital in healthy cats. *Journal of Feline Medicine and Surgery*. [Online] 2015. [Quoted in : 28/10/2021]. 17(4): 359–363. Available in: doi:10.1177/1098612X14545141

[13] Embu-Guaçu: União Química Farmacêutica Nacional S/A. *Phenobarbital : solução oral.* [Online] uniaoquimica. [Quoted in : 28/10/2021]. Available in: https://www.uniaoquimica.com.br/wp-content/uploads/2020/01/BULA-Phenobarbital -SOL-OR.pdf

[14]. Sanofi-Aventis Farmacêutica Ltda. Phenobarbital . *Bula de medicamento*.

[15] Laboratório Teuto Brasileiro S.A. *Phenobarbital | LABORATÓRIO TEUTO BRASILEIRO S/A*. buladeremedio.

[16] CRISTÁLIA Produtos Químicos Farmacêuticos Ltda. *Phenobarbital SÓDICO: solução injetável*. [Online] cristalia. [Quoted in : 28/10/2021]. Available in: https://www.cristalia.com.br/arquivos_medicamentos/215/215_Fenocris_Inj_Bula_Paciente.pdf

[17] CRISTÁLIA Produtos Químicos Farmacêuticos Ltda. *Phenobarbital : solução gotas*. [Online] Cristalia. [Quoted in : 28/10/2021]. : https://www.cristalia.com.br/arquivos_medicamentos/96/Fenocris_Bula_Profissional%20-%20solucao%20gostas.pdf

[18] Taylor SM. Seizures and Other Paroxysmal Events. *Small Animal Internal Medicine*. Missouri: Elsevier; 2020. p. 1100–1102.

[19] Thomas WB, Dewey CW. Seizures and Narcolepsy. *Practical Guide to Canine and Feline Neurology*. New Jersey: Wiley Blackwell.; 2015. p. 254–255.

[20] Bil RL. *Clinical Pharmacology and Therapeutics for Veterinary Technicians,*. 4th ed. vetbooks.ir. Missouri: Elsevier; 2016.

[21] Bunch SE, Conway MB, Center SA, Castleman WL, Baldwin BH, Hornbuckle WE, et al. Toxic hepatopathy and intrahepatic cholestasis associated with phenytoin administration in combination with other anticonvulsant drugs in three dogs. *Journal of the American Veterinary Medical Association*. [Online] 1987. [Quoted in : 28/10/2021] .190(2): 194–198. : https://pubmed.ncbi.nlm.nih.gov/3818433/

[22]. Massone F. *Anestesiologia veterinária: farmacologia e técnicas*. 5th ed. Rio de Janeiro: Guanabara Koogan; 2008

[23]. Bersan E, Volk HA, Ros C, Risio LD. Phenobarbitone-induced haematological abnormalities in idiopathic epileptic dogs: prevalence, risk factors, clinical presentation and outcome. *Veterinary Record*. [Online] 2014. [Quoted in : 28/10/2021]. 175(10): 247–247. : doi:10.1136/vr.102158