

Date of Approval: September 6, 2023

# FREEDOM OF INFORMATION SUMMARY

## APPLICATION FOR CONDITIONAL APPROVAL

Application number 141-578

FIDOQUEL™-CA1

(phenobarbital tablets)

Dogs

FIDOQUEL™-CA1 (phenobarbital tablets) are indicated for the control of seizures associated with idiopathic epilepsy in dogs

Sponsored by:

Genus Lifesciences Inc.

## **Executive Summary**

FIDOQUEL™-CA1 (phenobarbital tablets) is conditionally approved for the control of seizures associated with idiopathic epilepsy in dogs.

An animal drug that addresses a serious or life-threatening disease, or addresses an unmet animal or human health need, for which demonstrating effectiveness would require a complex or particularly difficult study or studies is eligible for expanded conditional approval. Idiopathic epilepsy (IE) has a morbidity that substantially impacts day-to-day functioning in dogs. Therefore, the conditionally approved use addresses a serious or life-threatening disease. Also, based on the unpredictability of the occurrence or outcome of IE, and the need for advanced or complicated tests to diagnose the disease, demonstrating effectiveness would require a complex or particularly difficult study or studies. Therefore, the Food and Drug Administration (FDA) determined that FIDOQUEL™-CA1 met the eligibility criteria for expanded conditional approval.

### **Safety and Reasonable Expectation of Effectiveness**

The sponsor used published literature to demonstrate that FIDOQUEL™-CA1 at the conditionally approved dose has a reasonable expectation of effectiveness for controlling seizures associated with IE in dogs.

A systematic review of published literature was performed to critically evaluate and summarize the available information on the safety of phenobarbital in dogs. Safety was bridged between FIDOQUEL™-CA1 and commercially available oral formulations of phenobarbital based upon published literature and formulation comparisons of qualitative, quantitative, and dissolution data.

The adverse reactions that were most consistently reported in the literature are lethargy or sedation, ataxia, polyphagia, polyuria, and polydipsia. These adverse reactions are generally seen either after first starting treatment or when the initial dose is too high. Additionally, the reactions tend to diminish within 10 days to 2 weeks after starting treatment because dogs usually develop tolerance. Overall, many of the adverse reactions are seen during longer-term administration and/or at high serum phenobarbital levels (> 35 mcg/mL). Veterinarians should closely monitor the clinical signs of each dog because plasma levels alone may not be the best predictor of how each patient will tolerate the drug.

The liver is the target organ for toxicity, but serious liver toxicity is rare. In most cases, phenobarbital-related hepatotoxicity is reversible by either stopping the drug or reducing the dose. Dogs with decreased liver function may be predisposed to phenobarbital toxicosis due to cytochrome P450 enzyme activation. Veterinarians should carefully monitor each patient to minimize the risk of liver injury.

The sponsor conducted a margin of safety study in healthy, adult dogs that were treated with 1X (5 mg/kg), 3X (15 mg/kg), and 5X (25 mg/kg) the maximum conditionally approved dose of phenobarbital administered orally twice daily. The study was terminated after 2 weeks due to acute toxicities and mortality in the 3X and 5X groups. The toxicities observed in these groups were central nervous system (CNS)-related, including severe sedation and ataxia (recumbent and non-responsive progressing to

moribund) after three doses were administered. Dogs in the 1X group did well throughout the two weeks of the study.

A retrospective study of data from a poison control center included dogs that ingested phenobarbital alone at a dose of  $\leq 5$  mg/kg. The most commonly reported adverse reactions were drowsiness or lethargy, ataxia, agitation or irritability, vocalization, inability to rise, and vomiting. The lowest dose associated with a serious adverse reaction was 14.3 mg/kg which is almost 3X the maximum conditionally approved dose. Serious adverse reactions included respiratory arrest, cardiac arrest, euthanasia, coma (unresponsive), and death.

### **User Safety**

As a barbiturate, phenobarbital is a Schedule IV controlled substance. Therefore, the labeling for FIDOQUEL™-CA1 contains information about drug abuse, addiction, and diversion. Because phenobarbital may cause developmental effects, women who are pregnant or may become pregnant should use caution when administering FIDOQUEL™-CA1 to dogs.

### **Conclusions**

Based on the data submitted by the sponsor for the conditional approval of FIDOQUEL™-CA1, FDA determined that the drug is safe and has a reasonable expectation of effectiveness when used according to the labeling.

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**I. GENERAL INFORMATION**

**A. File Number**

Application number 141-578

**B. Sponsor**

Genus Lifesciences Inc.  
700 North Fenwick Street  
Allentown, PA 18109

Drug Labeler Code: 064950

**C. Proprietary Name**

FIDOQUEL™-CA1

**D. Drug Product Established Name**

phenobarbital tablets

**E. Pharmacological Category**

Antiepileptic

**F. Dosage Form**

Tablet

**G. Amount of Active Ingredient**

16.2, 32.4, 64.8, or 97.2 mg per tablet

**H. How Supplied**

FIDOQUEL-CA1 tablets are unflavored, bisected tablets containing 16.2, 32.4, 64.8, and 97.2 mg phenobarbital per tablet and are packaged in bottles of 100 or 1000 tablets.

**I. Dispensing Status**

Prescription (Rx)

**J. Dosage Regimen**

FIDOQUEL™-CA1 is given orally twice a day at the minimum dosage of 2.5 mg/kg (5 mg/kg/day) and may be titrated to effect to a maximum dosage of 5 mg/kg (10 mg/kg/day). The dosage of FIDOQUEL™-CA1 should be adjusted based on monitoring of the clinical response of the individual patient. FIDOQUEL™-CA1 should be dosed with food.

**K. Route of Administration**

Oral

**L. Species/Class**

Dogs

**M. Indication**

FIDOQUEL™-CA1 (phenobarbital tablets) are indicated for the control of seizures associated with idiopathic epilepsy in dogs.

**II. EFFECTIVENESS**

**Conditional Dose:** The conditional dose for the indication for the control of seizures associated with idiopathic epilepsy in dogs is a minimum dosage of 2.5 mg/kg (5 mg/kg/day) administered orally twice a day. The dose may be titrated to effect to a maximum dosage of 5 mg/kg (10 mg/kg/day). The dosage of FIDOQUEL™-CA1 should be adjusted based on monitoring of the clinical response of the individual patient. The safety data and the data to demonstrate reasonable expectation of effectiveness provide support for this conditional dose.

**A. Dosage Characterization**

The dosing regimen for FIDOQUEL™-CA1, administered orally twice a day at the minimum dosage of 2.5 mg/kg (5 mg/kg/day) and titrated to effect to a maximum dosage of 5 mg/kg (10 mg/kg/day) based on monitoring of clinical response of the individual patient, is supported by nine publications in the scientific literature. Refer to the Reasonable Expectation of Effectiveness section for more information.

**B. Reasonable Expectation of Effectiveness**

Reasonable expectation of effectiveness for phenobarbital for the control of seizures associated with idiopathic epilepsy (IE) in dogs is based on published literature. The supportive publications include two current clinical consensus statements on seizure management in dogs, published by the American College of Veterinary Internal Medicine (Podell et al., 2016) and the International Veterinary Epilepsy Task Force (Bhatti et al, 2015). The supportive published literature for the effectiveness of phenobarbital treatment also includes six published clinical studies, including four randomized, prospective, comparator studies in dogs with seizures (Schwartz-Porsche et al., 1985; Boothe et al., 2012; Tipold et al., 2014; Fredsø et al., 2016), and two retrospective studies (presented in three publications) of veterinary records (Heynold et al., 1997; Löscher et al., 2004; Rieck et al., 2006). These publications collectively support that phenobarbital at the conditionally approved dose has a reasonable expectation of effectiveness for controlling seizures associated with IE in dogs.

1. Podell, M., Volk, H. A., Berendt, M., Löscher, W., Muñana, K., Patterson, E. E., and Platt, S. R. (2016). 2015 ACVIM small animal consensus statement on

seizure management in dogs. *Journal of veterinary internal medicine*, 30(2), 477-490.

This clinical consensus statement is based on literature and clinical expertise and was written to provide a concise sequential approach to chronic seizure management in dogs. The American College of Veterinary Internal Medicine (ACVIM) consensus statement reviewed 8 studies including a total of 311 dogs where seizure reduction was evaluated following phenobarbital monotherapy. Over the 8 studies, 82% of the dogs (258/311 dogs) had > 50% seizure reduction, 31% (93/311) were seizure-free, and 15% (48/311) of dogs did not improve. The ACVIM panel gave phenobarbital their highest recommendation for an antiepileptic drug (AED) monotherapy, meaning that phenobarbital is likely to be effective based on evaluation of blinded, randomized clinical trials, and  $\geq 50\%$  decrease in seizure frequency for at least 6 months with continued dosing. The panel recommended that phenobarbital should be administered orally at a starting dose of 2.5 mg/kg every 12 hrs. Adjustments to the dose may be made based on each patient's clinical response and tolerance to the drug. The panel stated that the most effective and safe therapeutic range for phenobarbital serum concentration is 15-35  $\mu\text{g/mL}$ , although effectiveness can be seen at lower concentrations.

2. Bhatti, S. F., De Risio, L., Muñana, K., Penderis, J., Stein, V. M., Tipold, A., Berendt, M., Farquhar, R., Fischer, A., Long, S., Löscher, W., Mandigers, P., Matiasek, K., Pakozdy, A., Patterson, E., Platt, S., Podell, M., Potschka, H., Rusbridge, C., and Volk, H. A. (2015). International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe. *BMC veterinary research*, 11(1), 1-16.

This consensus statement is based on published evidence-based literature, and reflects the authors' clinical experience, with the aim to provide a consensus for the management of canine idiopathic epilepsy. The task force consensus proposal states that phenobarbital has a favorable pharmacokinetic profile, is relatively safe, and, when serum phenobarbital concentration is maintained within the therapeutic range of 25-35  $\mu\text{g/mL}$  serum, it is 60-93% effective in decreasing seizure frequency in dogs with IE. The task force consensus proposal recommends an oral starting dose of 2.5-3.0 mg/kg twice daily and adjusting the dose to the individual dog based on seizure control, adverse effects, and serum concentration monitoring.

3. Schwartz-Porsche, D., Löscher, W., & Frey, H. H. (1985). Therapeutic efficacy of phenobarbital and primidone in canine epilepsy: a comparison. *Journal of veterinary pharmacology and therapeutics*, 8(2), 113-119.

The effectiveness of phenobarbital and primidone to control seizures in dogs with epilepsy was compared in a controlled field study. Thirty-five dogs suffering from generalized seizures were treated for a minimum of 6 months; 15 of these dogs were treated with phenobarbital and 20 with primidone. Both drugs were dosed according to the clinical practice of the individual investigators: the daily phenobarbital doses ranged from 5-17 mg/kg, and the daily primidone doses

ranged from 17-70 mg/kg. The plasma concentrations of phenobarbital, or of primidone and its metabolites (phenobarbital and phenylethylmalondiamide [PEMA]), were routinely monitored.

Complete eradication of seizures for at least 6 months was achieved in 6 out of 15 dogs treated with phenobarbital and in 5 out of 20 dogs treated with primidone. An additional 6 dogs on phenobarbital and 7 dogs on primidone were classified as 'improved' ( $\geq 50\%$  reduction in seizure frequency). The rest of the dogs did not improve with the treatment. The difference between the effectiveness of phenobarbital and primidone was not significant. However, 14 out of 20 dogs treated with primidone showed clinical pathology changes consistent with liver toxicity, as indicated by significant elevations of serum levels of alanine transferase, glutamate dehydrogenase, and alkaline phosphatase. One dog treated with phenobarbital demonstrated similar clinical pathology changes, though to a lesser degree.

4. Boothe, D. M., Dewey, C., & Carpenter, D. M. (2012). Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs. *Journal of the American Veterinary Medical Association*, 240(9), 1073-1083.

The objective of this double-blind, randomized, clinical field study was to compare the safety and effectiveness of phenobarbital versus bromide as the first-choice AED in dogs. Forty-six AED-naïve dogs with naturally occurring epilepsy were treated with phenobarbital (21 dogs) or bromide (25 dogs). Study inclusion was based on age, history, findings on physical and neurologic examinations, and clinical pathology test results. For either treatment, a 7-day loading dose period was initiated (4.4 mg/kg phenobarbital or 47.1 mg/kg bromide every 12 hours) followed by a maintenance dose (3.5 mg/kg phenobarbital or 15 mg/kg bromide every 12 hours), which was adjusted on the basis of monthly monitoring.

Phenobarbital treatment resulted in the eradication of seizures (17/20 [85%]) significantly more often than did bromide (12/23 [52%]). Phenobarbital treatment also resulted in a greater percentage decrease in seizure duration ( $88 \pm 34\%$ ; mean  $\pm$  standard deviation) compared with bromide ( $49 \pm 75\%$ ). Seizure activity worsened in 3 bromide-treated dogs only. In dogs with seizure eradication, the mean  $\pm$  standard deviation (SD) serum phenobarbital concentration was  $25 \pm 6$   $\mu\text{g/mL}$  (mean  $\pm$  SD oral phenobarbital dosage was  $4.1 \pm 1.1$  mg/kg every 12 h) and serum bromide concentration was  $1.8 \pm 0.6$  mg/mL (oral bromide dosage was  $31 \pm 11$  mg/kg every 12 h). Compared to bromide-treated dogs, ataxia, lethargy, and polydipsia were greater at 1 month for phenobarbital-treated dogs. Vomiting was greater for bromide treated dogs at 1 month and study end compared to phenobarbital-treated dogs.

5. Tipold, A., Keefe, T. J., Löscher, W., Rundfeldt, C., & De Vries, F. (2015). Clinical efficacy and safety of imepitoin in comparison with phenobarbital for the control of idiopathic epilepsy in dogs. *Journal of veterinary pharmacology and therapeutics*, 38(2), 160-168.



The safety and effectiveness of imepitoin, an antiepileptic drug licensed in the European Union for use in dogs, was compared to phenobarbital in 226 client-owned dogs in a multicenter, blinded, field effectiveness study. Dogs with newly diagnosed idiopathic epilepsy and with at least 2 generalized convulsive seizures within a documented retrospective 6-week baseline period were eligible for enrollment in the study. The phenobarbital group received an initial dose of 2 mg/kg phenobarbital twice daily, which could be increased to 4 mg/kg twice daily and, if required, to 6 mg/kg twice daily, if the seizures were considered to be uncontrolled at the lower dose. Imepitoin was administered twice daily in incremental doses of 10, 20, or 30 mg/kg.

One hundred and ten enrolled dogs were started on phenobarbital and 116 on imepitoin. Of these, 88 dogs treated with phenobarbital and 64 with imepitoin were included in evaluation of effectiveness. Five dogs in each group were withdrawn by the owners due to adverse events. At the conclusion of the study, 73.9% of dogs were well controlled when administered 2 mg/kg phenobarbital twice daily throughout the study, while 9.1% of dogs reached the highest dose of 6 mg/kg twice daily. The mean dose for all dogs in the group was 2.7 mg/kg of phenobarbital twice daily. The percent of dogs in the phenobarbital treatment group with a  $\geq 50\%$  reduction in monthly seizure frequency was 83% (73/88). Additionally, the percent of dogs in phenobarbital treatment group with complete eradication of generalized seizures was 58.0% (51/88).

The frequency of adverse events including somnolence/sedation, polydipsia, and increased appetite was significantly higher in the phenobarbital group. In phenobarbital-treated dogs, significantly increased levels of alkaline phosphatase, gamma-glutamyl transferase, and other liver enzymes occurred, while no such effect was observed in the imepitoin group.

6. Fredsø, N., Sabers, A., Toft, N., Møller, A., & Berendt, M. (2016). A single-blinded phenobarbital-controlled trial of levetiracetam as monotherapy in dogs with newly diagnosed epilepsy. *The Veterinary Journal*, 208, 44-49.

The safety and effectiveness of levetiracetam and phenobarbital as monotherapy in dogs with idiopathic epilepsy was investigated in a prospective, single-blinded, parallel group design study. Twelve client-owned dogs were randomized to treatment with levetiracetam (30 mg/kg/day or 60 mg/kg/day divided into three daily dosages) or phenobarbital (4 mg/kg/day divided twice daily). If 2 or more seizures occurred within 3 months, the drug dosage was increased by 10 mg/kg/day for levetiracetam or 1 mg/kg/day for phenobarbital.

Five of 6 levetiracetam treated dogs and 1 of 6 phenobarbital treated dogs withdrew from the study within 2-5 months due to insufficient seizure control. In the levetiracetam treated dogs there was no significant difference in the monthly number of seizures before and after treatment, whereas in the phenobarbital treated dogs there were significantly ( $P = 0.013$ ) fewer seizures after treatment. Five phenobarbital treated dogs had a  $\geq 50\%$  reduction in seizure frequency per month. At study conclusion, the dose for individual dogs ranged 4.3-6 mg/kg/day (divided into two doses) for phenobarbital.

Adverse events were reported in both groups but were more frequent in the phenobarbital group. In the phenobarbital group the most common adverse events (reported by  $\geq 50\%$  of owners) were polyphagia, polydipsia, polyuria, weight gain, sedation, restlessness, and decreased activity. One dog treated with phenobarbital and 2 dogs treated with levetiracetam experienced cluster seizures.

7. Heynold, Y., Faissler, D., Steffen, F., & Jaggy, A. (1997). Clinical, epidemiological and treatment results of idiopathic epilepsy in 54 Labrador retrievers: a long-term study. *Journal of Small Animal Practice*, 38(1), 7-14.

The records of 54 Labrador retrievers with idiopathic epilepsy were reviewed. Prior to initiating any antiepileptic treatment, approximately half of the dogs had seizures more than once a month; the remainder ranged from 1 every 2 months to 1 every 12 months. The average seizure frequency in dogs with generalized seizures ( $n = 49$ ) was 1 every 65 days and in dogs with partial seizures ( $n = 5$ ) was 1 every 205 days. None of the dogs had been treated with antiepileptic drugs before presentation.

Long-term follow-up (8-108 months) was performed in 46 dogs. Thirty-seven dogs started treatment with phenobarbital at a dose of 2-2.5 mg/kg bodyweight administered orally twice a day. The phenobarbital serum levels were measured 3 to 4 weeks after start of therapy, and the dosage for each dog was adjusted until serum concentrations were within the range of 15 to 40  $\mu\text{g/ml}$ . Based on serum level measurements, the phenobarbital dose was reduced to 1-1.5 mg/kg twice daily in 4 dogs, increased to 3 and 5 mg/kg twice daily in 1 and 7 dogs, respectively, and not changed in 25 dogs. Phenobarbital treatment resulted in eradication of seizures in 11 dogs and seizure improvement (decreased frequency, severity, and/or duration of seizures) in 16 dogs. Ten dogs demonstrated no change with phenobarbital treatment. Twenty-four dogs showed no side effects of phenobarbital treatment, whereas 13 dogs presented with fatigue ( $n = 10$ ), ataxia ( $n = 2$ ), polyphagia ( $n = 1$ ), itching ( $n = 1$ ), or periods of aggressiveness ( $n = 1$ ). No correlation was found between the appearance of side effects and a mild elevation of liver enzymes seen in 14 dogs.

The course of the disease in the 9 untreated dogs was followed for an average time of 4.0 years (range, 15-83 months). In 6 of these dogs, a progression of clinical signs was observed which was characterized by an increase in the frequency of seizures (mean, 20%) in 5 dogs and/or a prolonged duration of seizures (mean, 25%) in 3 dogs.

8. Löscher, W., Potschka, H., Rieck, S., Tipold, A., & Rundfeldt, C. (2004). Anticonvulsant efficacy of the low-affinity partial benzodiazepine receptor agonist ELB 138 in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures. *Epilepsia*, 45(10), 1228-1239.

An experimental antiepileptic and anxiolytic drug, ELB138, was evaluated in clinical studies in dogs with newly diagnosed or chronic idiopathic epilepsy. The results were compared with those obtained retrospectively from 82 dogs treated

with conventional antiepileptic medication: Forty-four dogs were treated with phenobarbital monotherapy (mean dose 6.0 mg/kg/day; range 4-13), 26 dogs with primidone monotherapy, and 12 dogs with potassium bromide in addition to phenobarbital or primidone. Four of the 12 (33%) dogs treated with ELB138 alone demonstrated  $\geq 50\%$  reduction of seizures, with 1/12 (8%) having complete seizure eradication; 3/12 (25%) were non-responders. In contrast 28/44 (64%) of the dogs treated with phenobarbital, and 16/26 of the dogs treated with primidone (62%) demonstrated  $\geq 50\%$  reduction of seizures, with 9/44 (20%) and 4/26 (15%) having complete seizure eradication, respectively; 27% of the dogs were non-responders in both phenobarbital and primidone treated groups.

9. Rieck, S., Rundfeldt, C., & Tipold, A. (2006). Anticonvulsant activity and tolerance of ELB138 in dogs with epilepsy: a clinical pilot study. *The Veterinary Journal*, 172(1), 86-95.

Note: Löscher et al., (2004) and Rieck et al., (2006) review the same study and are summarized together above.

### III. TARGET ANIMAL SAFETY

A weight of evidence approach was used to determine the safety of FIDOQUEL™-CA1. To bridge safety data from the published literature, FIDOQUEL™-CA1 was compared to the commercially available oral formulations of phenobarbital with qualitative and quantitative comparisons of the formulations and dissolution data. All formulations evaluated were qualitatively and quantitatively similar to FIDOQUEL™-CA1. The dissolution of FIDOQUEL™-CA1 and the commercially available oral formulations of phenobarbital was rapid with greater than 85% dissolved within 15 minutes. FIDOQUEL™-CA1 was determined to have comparable in vivo bioavailability and pharmacokinetic performance in dogs to the commercially available oral formulations of phenobarbital included in the published literature used to demonstrate safety.

#### A. Published Literature Review – Phenobarbital Safety

A systematic review of the published literature containing data describing the target animal safety of phenobarbital was performed.

The objective of this systematic review was to critically evaluate and summarize the available information on the safety of phenobarbital in dogs. PubMed and Toxline searches without date limitations were conducted with the terms “phenobarbital”, “safety”, and “toxicity” in both animals and dogs, in various combinations. Accordingly, multiple individual search terms and combinations of search terms were used to identify articles that could be used to support the evaluation of safety for phenobarbital in dogs.

The most consistently reported toxicoses, generally seen either initially after the start of treatment or when the initial dose is too high, are lethargy/sedation, ataxia, polyphagia, and polyuria/polydipsia. These adverse findings usually diminish within 10 days to 2 weeks of the start of therapy because tolerance to these effects generally develops. Occasionally aggression and behavior changes are reported. It

is generally noted that sedation and ataxia improve or resolve within the first few weeks to months of treatment.<sup>i,ii,iii,iv,v,vi</sup> Polyphagia often persists and can result in weight gain over time. Mild to moderate increases in alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), and glutamate dehydrogenase (GLDH) indicate that the liver is the target organ for toxicity. However, these effects are reversible with a reduction in dose or discontinuation of treatment. Serious liver toxicity is rare and more likely associated with chronic use or phenobarbital serum concentrations > 35 mcg/ml. Studies have found that serum aspartate transaminase (AST), fasted bile acids (fBA), and bilirubin, as well as ultrasonographic evaluation of the liver, are not as affected by the enzyme-inducing effect of phenobarbital. Therefore, monitoring these parameters can be helpful to assess liver disease in dogs treated with the drug.<sup>vii,viii</sup>

Phenobarbital-induced hematological abnormalities (neutropenia, anemia, thrombocytopenia) have been reported and are considered an idiosyncratic, non-dose-dependent reaction.<sup>ix</sup>

Dermatologic abnormalities (pruritus, alopecia, papules, pustules, erythema, and rarely epidermal necrosis) and subclinical changes in thyroid hormone levels (decreased T4, increased TSH) may occur in dogs treated with phenobarbital. Lymphadenopathy, tremors, hypoadrenocortical crisis, and pancreatitis have also been reported.

Overall, much of the toxicity reported in the literature is seen during longer term administration and at high serum phenobarbital levels (> 35 mcg/ml). In addition, it is important to monitor clinical signs of individual animals because plasma levels alone may not be the best predictor of how each patient will tolerate the drug. Veterinarians should tailor therapeutic regimens and clinical monitoring to each dog. Animals with decreased liver function may be predisposed to phenobarbital toxicosis due to activation of cytochrome P450 enzyme induction. Careful monitoring of each patient is required to minimize the risk of liver injury. Examples of drugs that may be affected by the effects of phenobarbital on cytochrome P450 enzymes are rifampin, omeprazole, chloramphenicol, digoxin, and propranolol.<sup>x</sup> Phenobarbital related hepatotoxicity appears to be reversible in most cases with either discontinuation or a reduction in the phenobarbital dose.

## **B. Other safety information**

A margin of safety study, using twice daily phenobarbital doses of 5 mg/kg, 15 mg/kg, and 25 mg/kg, was terminated after 2 weeks due to acute toxicities and mortality in the high dose groups. The toxicities observed in the two highest dose groups were CNS-related, including severe sedation and ataxia (recumbent and non-responsive progressing to moribund) after three doses were administered. Dogs in the lowest dose group (5 mg/kg), did well throughout the two weeks of the study.

A retrospective study of data on 1083 cases from a poison control center included 268 dogs that ingested phenobarbital alone at a dose of ≤ 5 mg/kg. Among the 22 dogs with at least one symptom, the following were most commonly reported findings: drowsiness/lethargy, ataxia, agitated/irritable, vocalization, unable to rise,

and vomiting. Serious adverse events were reported in 50 of 1083 dogs (4.6%), and 43 of these 50 dogs received doses > 25 mg/kg (> 5X). The lowest dose associated with a serious adverse event was 14.3 mg/kg which represents a dose level of 2.9X the highest recommended dose. Serious adverse events included respiratory arrest, cardiac arrest, euthanasia, coma (unresponsive), and death.

#### **IV. HUMAN FOOD SAFETY**

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for conditional approval of this application.

#### **V. USER SAFETY**

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to FIDOQUEL™-CA1:

##### **Human Safety Warnings**

Not for use in humans. Keep this and all medications out of reach of children.

**Because phenobarbital may cause developmental effects, women who are pregnant or may become pregnant should administer FIDOQUEL™-CA1 with caution.**

##### **Human User Safety While Handling FIDOQUEL™-CA1**

Mucous Membrane Contact, Eye Contact, or Accidental Ingestion:

In case of accidental ingestion, skin reaction, or eye exposure, contact a physician immediately.

If accidental eye contact or mucous membrane exposure occurs, rinse the exposed area thoroughly.

Skin Contact:

Users should wash skin exposed to the drug, including washing their hands thoroughly after contacting the drug.

##### **Drug Abuse, Addiction, and Diversion**

Controlled Substance:

FIDOQUEL™-CA1 contains phenobarbital, a Schedule IV controlled substance.

Abuse: Phenobarbital is a barbiturate and a central nervous system (CNS) depressant with a potential for misuse, abuse, and addiction. Abuse is defined as the intentional, non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Abuse and misuse of barbiturates often (but not always) involve the use of doses exceeding the doses used in clinical practice and commonly involve concomitant use of

other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death. Barbiturates, including phenobarbital, are often sought by individuals who abuse drugs and other substances, and by individuals with addictive disorders.

Symptoms of acute intoxication with barbiturates include unsteady gait, slurred speech, and sustained nystagmus. Mental signs of chronic intoxication include confusion, poor judgment, irritability, insomnia, and somatic complaints. The use of phenobarbital alone can result in death; however, death is more often associated with phenobarbital use in the context of polysubstance use (especially with other CNS depressants, such as opioids and alcohol).

Phenobarbital may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Abrupt discontinuation or rapid dosage reduction of phenobarbital may precipitate acute withdrawal reactions, including seizures, which can be life-threatening.

Tolerance may occur with continued use. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than twofold. As this occurs, the margin between intoxicating dosage and fatal dosage becomes smaller.

Consider the potential risks of misuse or abuse before prescribing this product. Signs of phenobarbital misuse or abuse include drug seeking behavior.

Diversion: FIDOQUEL™-CA1 is a Schedule IV antiepileptic and should be handled appropriately to minimize the risk of diversion, including restriction of access, the use of accounting procedures, and proper disposal methods. Store in a locked cabinet according to federal and state controlled substance requirements and guidelines. Any unused or expired bottles must be destroyed by a reverse distributor. For further information, contact your local DEA field office or call Genus Lifesciences Inc.

**Note to physician:** FIDOQUEL™-CA1 contains phenobarbital.

## VI. AGENCY CONCLUSIONS

The data submitted in support of this application satisfy the requirements of section 571(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The data demonstrate that FIDOQUEL™-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the control of seizures associated with idiopathic epilepsy in dogs.

### A. Conditional Approval Eligibility

In 2018, the legislation reauthorizing FDA's animal drug user fee program (Animal Drug User Fee Program, or ADUFA, IV) expanded the conditional approval pathway to allow certain additional new animal drugs that are not Minor Use/Minor Species

(MUMS) drugs to be eligible for conditional approval. As provided in section 571(a)(1)(A)(ii) of the FD&C Act, as amended by ADUFA IV, to qualify for conditional approval, the non-MUMS new animal drug must meet the following two criteria:

1. The new animal drug is intended to treat a serious or life-threatening disease or condition OR addresses an unmet animal or human health need; AND
2. A demonstration of effectiveness would require a complex or particularly difficult study or studies.

FIDOQUEL™-CA1 was determined to be eligible for conditional approval under these provisions because it controls a serious or life-threatening disease or condition, addresses an unmet animal health need, and the demonstration of effectiveness requires a complex or particularly difficult study or studies. Idiopathic epilepsy in dogs is a disease associated with morbidity that has substantial impact on day-to-day functioning. Therefore, the conditionally approved use addresses a serious or life-threatening disease or condition. The control of idiopathic epilepsy in dogs was also determined to be an unmet animal health need because there is no drug approved under a new animal drug application (NADA) that is currently being marketed in the United States for this use in dogs. Finally, based on the unpredictability of the occurrence or outcome of the disease, and the need for use of advanced or complicated tests to diagnose idiopathic epilepsy, it was determined that the demonstration of effectiveness requires a complex or particularly difficult study or studies.

#### **B. Marketing Status**

FIDOQUEL™-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional veterinary expertise is required to diagnose idiopathic epilepsy and to monitor safe use of the product, including treatment of any adverse reactions.

#### **C. Exclusive Marketing Rights**

FIDOQUEL™-CA1 as approved in our approval letter, does not qualify for exclusive marketing rights under section 573(c) of the FD&C Act because it is not a designated new animal drug under section 573(a) of the FD&C Act.

#### **D. Patent Information**

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.

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- <sup>x</sup> Trepanier, Cytochrome P450 and Its Role in Veterinary Drug Interactions, *Veterinary Clinics of North America: Small Animal Practice*, Volume 36, Issue 5, 2006, Pages 975-985, ISSN 0195-5616