

Date of Approval: December 4, 2018

**FREEDOM OF INFORMATION SUMMARY**  
**ORIGINAL NEW ANIMAL DRUG APPLICATION**

NADA 141-509

Pexion™

(imepitoin tablets)

Dogs

For treatment of noise aversion in dogs.

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

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**I. GENERAL INFORMATION**

**A. File Number**

NADA 141-509

**B. Sponsor**

Boehringer Ingelheim Vetmedica, Inc.,  
2621 North Belt Highway,  
St. Joseph, MO 64506-2002

Drug Labeler Code: 000010

**C. Proprietary Name**

Pexion™

**D. Drug Product Established Name**

Imepitoin tablets

**E. Pharmacological Category**

GABA<sub>A</sub> receptor partial agonist

**F. Dosage Form**

Tablet

**G. Amount of Active Ingredient**

100 mg and 400 mg imepitoin per tablet

**H. How Supplied**

Pexion™ tablets are supplied as white single-scored oblong tablets in bottles of 100 or 250 tablets.

**I. Dispensing Status**

Rx

**J. Dosage Regimen**

Pexion™ should be administered orally at a dose of 13.6 mg/lb (30 mg/kg) of body weight twice daily, approximately 12 hours apart using a suitable combination of whole and half tablets. Initiate therapy starting 2 days prior to the day of the expected noise event, and continuing through the noise event.

**K. Route of Administration**

Oral

## **L. Species/Class**

Dogs

## **M. Indication**

Pexion™ tablets are indicated for treatment of noise aversion in dogs.

## **II. EFFECTIVENESS**

The effectiveness of Pexion™ was demonstrated in one adequate and well-controlled clinical field study. Pexion™ was administered to 238 client-owned dogs. The most common adverse reactions were ataxia, increased appetite, lethargy, and emesis. Three adverse reactions were reported as aggression. Anxiolytic drugs acting at the benzodiazepine receptor site, including imepitoin, may lead to disinhibition of fear-based behaviors and may therefore result in a change in aggression level. Careful observation by the owners is recommended during treatment. The field study demonstrated that Pexion™ was effective for the treatment of acute behavior abnormalities associated with noise aversion in dogs when administered at 30 mg/kg body weight twice daily starting 2 days prior to the day of the expected noise event, and continuing through the noise event. While the pharmacokinetic study (see Section III.B) determined that systemic exposure is greater in fasted dogs, the field studies support the effectiveness of imepitoin in either a fed or fasted state.

### **A. Dosage Characterization**

The targeted dose of 30 mg/kg body weight twice daily starting 2 days prior to the day of the expected noise event, and continuing through the noise event, is supported by pilot field studies, non-clinical laboratory studies, and pharmacokinetic studies.

#### **Exploratory Pilot Field Studies**

##### **Pilot field study in dogs with generalized anxiety disorder**

The use of short term treatment with imepitoin (20 mg/kg body weight orally twice daily for three days) on a group of dogs identified as suffering from generalized anxiety disorder was evaluated in a prospective, placebo-controlled, randomized, double-blinded, single-site field study. Sixty dogs with generalized anxiety disorder were treated with imepitoin or placebo. Before and after treatment, behavioral tests on various aspects of reaction to anxiogenic stimuli and measurement of blood cortisol levels were performed.

After three days of treatment, the relative cortisol levels of imepitoin treated dogs were reduced, whereas cortisol levels of control dogs were increased, resulting in a significant difference in the change of cortisol levels between the treatment groups. While this suggests a reduction of the existing stress levels in dogs administered imepitoin, no change in anxiety behavior, as measured by the behavioral scores on the day of inclusion and after three days of treatment, in response to anxiogenic stimuli were detected in this study.

In total 35 adverse events (AEs) were recorded during this study in 25 of the 60 dogs (17 AEs in 13 dogs administered imepitoin; 18 AEs in 12 control dogs). None of the observed adverse events was classified as serious. In imepitoin-

treated dogs, ataxia was the most frequently reported adverse event (6 reports) followed by hyperactivity and fatigue (3 reports each). The observed effects of the administration of imepitoin on cortisol levels in dogs identified as suffering from generalized anxiety disorder suggest an effect on the stress response in the presence of a fear triggering stimulus.

#### **Pilot field study in dogs with various anxiety disorders**

The second pilot field study was designed to investigate the potential value of imepitoin for long term treatment (minimum 11 weeks) in a group of dogs experiencing a range of fear and anxiety related problems. The study evaluated the use of imepitoin alongside an individualized behavior modification program in 17 dogs identified as having different fear and anxiety-based problems. Eliciting contexts included both social and non-social triggers, with aversion to noises being most frequent. All cases began the study receiving a dose of approximately 10 mg/kg body weight twice daily. Depending on the dog's progress during the study, dose alterations were made up to a maximum of 30 mg/kg body weight twice daily. Most of the dogs received 20 mg/kg body weight (10/17; 59%) or 30 mg/kg body weight (4/17; 24%) twice daily.

Treatment with imepitoin, in combination with a behavior modification program, reduced the average weekly global scores (modified Lincoln Sound Sensitivity Scale) across a range of eliciting contexts as reported by owners. Improvement was observed within the first week of treatment, but was more pronounced at the end of study. Improvement was also noted for all evaluated subgroups of eliciting contexts including social fear and anxiety, non-social fear and anxiety (excluding noise sensitivity), and noise sensitivity. Most owners (> 70%) were satisfied or very satisfied by improvement in fear and anxiety behaviors at the end of the study.

Adverse events were reported in six dogs, with ataxia being the most frequently reported adverse event.

The observed effects of the administration of imepitoin at doses of 20 to 30 mg/kg body weight twice daily, in combination with an individualized behavior modification program, support its use in the treatment of noise aversion.

#### **Anxiety Model in Dogs**

To further characterize the required dose and the time between start of treatment and noise event, two laboratory dog studies were performed in a provoked open field sound-induced fear model. In this model, reactions to noises were elicited by a sound recording of thunder.

The results of both laboratory studies indicated that doses of 20 and 30 mg/kg body weight administered twice daily were appropriate for further examination in a clinical field setting. In the initial study, a single dose of 20 mg/kg body weight imepitoin given before a noise event had anxiolytic properties in fasted dogs as demonstrated by changes in activity level and behavior in a laboratory setting in response to noise stimuli. A second laboratory study was performed to determine dose regimen under conditions more representative of a field environment (e.g., more time between dosing and testing, feeding before dosing). In this study, imepitoin's anxiolytic effect was observed at doses of 20 and 30 mg/kg body weight, but the effect was more pronounced in the 30 mg/kg body weight group.

The effect increased after 3 to 4 days of treatment compared to treatment days 1 and 2. There were no safety concerns noted in either study.

Data from the two laboratory studies suggest that imepitoin is effective at a dosage of 30 mg/kg body weight twice daily when administered prior to the anxiety eliciting event. The shortest required time to achieve optimal effectiveness was shown to be two days before the day of the anticipated event.

## **B. Substantial Evidence**

**Type of Study:** Multi-site Field Effectiveness Study

**Title:** Clinical field efficacy study of imepitoin for the control of anxiety and fear associated with noise phobia in dogs (study no. 2015385)

**Study Dates:** October 2016 – September 2017

### **Study Locations:**

Alfter, Germany  
Bonn-Beuel, Germany  
Düsseldorf, Germany  
Essen, Germany  
Esslingen, Germany  
Haan, Germany  
Hannover, Germany  
Heilbronn, Germany  
Hennef, Germany  
Köln, Germany  
Köln (Mülheim), Germany  
Köln (Rodenkirchen), Germany  
Lohmar, Germany  
Mainz, Germany  
Mainz, Germany  
Peine, Germany  
Recklinghausen, Germany  
Amsterdam, Netherlands  
Enschede, Netherlands  
Oisterwijk, Netherlands  
Veldhoven, Netherlands

### **Study Design:**

**Study Objective:** To evaluate the safety and effectiveness of Pexion™ administered to client-owned dogs for the treatment of acute behavior abnormalities associated with noise aversion, using fireworks as the eliciting context. This study was conducted in accordance with Good Clinical Practices.

**Study Animals:** A total of 251 client-owned, male and female, pure and mixed breed dogs were randomized in the study. Of the randomized dogs, 238 received treatment with either imepitoin (114 dogs) or vehicle control (124 dogs). The age of the dogs ranged between 1 and 14 years and body weight ranged between 3

and 72 kg. All dogs were healthy or had stable systemic disease, and had previously demonstrated noise aversion behaviors due to fireworks as documented by their owners.

Treatment Groups: Dogs were randomized into two treatment groups in a 1:1 ratio of Pexion™ (30 mg/kg body weight) to control product.

Drug Administration: The Pexion™ group received the final market formulation of an orally administered tablet containing either 100 or 400 mg imepitoin, depending upon the weight of the dog. The control product was visually identical to the imepitoin tablets and only contained inactive ingredients. Each group was administered treatment directly into the mouth twice daily for two days leading up to the day of the noise event (New Year's Eve) and continuing through the event. Feeding was not restricted during the study, but owners were advised to keep the timing of tablet administration in relation to feeding consistent between doses.

Measurements and Observations: Dogs with diagnosed noise aversion based on the Lincoln Sound Sensitivity Scale<sup>1</sup> were eligible for study participation. A veterinarian examined the dog and interviewed the dog owner within 7 weeks of the baseline assessments. The owner performed the baseline assessments 4 days before New Year's Eve. Treatment was started two days before the anticipated noise event (December 29), either with imepitoin or vehicle control, and dogs were treated for a total of three days. The owner performed the safety assessments throughout the study and performed the effectiveness assessments on New Year's Eve (December 31), at fixed, representative time points (4:00 pm, 10:00 pm, 12:20 am, 1:00 am). The owner performed the assessment of the overall treatment effect on New Year's Day (January 1). A veterinarian again examined the dog during the first 3 weeks of January. The owner assessments were also reviewed at this visit.

There were two co-primary effectiveness variables evaluated in the study. The first co-primary variable was the overall effect of study treatment on noise aversion behaviors in dogs in response to fireworks on New Year's Eve compared to the reaction to fireworks in previous years without treatment. The second co-primary variable was the sum of behavior scores, measured at the fixed time points of 4:00 pm and 10:00 pm on December 31, and 12:20 am and 1:00 am on January 1.

For the first co-primary variable, the dog owner rated the overall effect of study treatment on behavior of the dog on January 1 compared to previous years without treatment. The dog owner assessed the treatment effect by using the scale presented in Table II.1.

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<sup>1</sup> Mills DS, Braem Dube M, Zulch H. Stress and Pheromonotherapy. *Small Animal Clinical Behaviour*. 1 ed. Chichester: Wiley-Blackwell; 2013, pp. 191-214 and 259-263.

**Table II.1. Owner assessment of the treatment effect on the behavior of dogs**

<b>Score</b>	<b>Description</b>
<b>Excellent Effect</b>	The dog does not react to fireworks with anxious/fearful behavior at all
<b>Good Effect</b>	The dog's reactions are mild and it can calm down
<b>Some Effect</b>	The dog is reacting somewhat less/milder than in previous year(s) without treatment, but it cannot calm down
<b>No Effect</b>	There is no reduction/change in the dog's reactions compared to previous year(s) without treatment
<b>Worse Effect</b>	The dog's reaction to fireworks is stronger than in previous year(s) without treatment

For the second co-primary variable, the dog owner assessed the extent, on a scale from 0 (not present) to 1 (small amount) through 5 (excessive amount) of the following 16 behaviors derived from the Lincoln Sound Sensitivity Scale: running around, drooling saliva, hiding (under furniture, behind owner, etc.), destructiveness (furniture, doors, carpets, etc.), cowering (tucks tail, flattens ears, etc.), restlessness or pacing, aggressive behavior (growling, snapping or biting), freezing to the spot, barking/whining/howling, panting, vomiting/defecation/urinating and/or diarrhea, owner seeking behavior, vigilance/scanning of the environment, bolting, shaking or trembling, and self-harm.

Safety was assessed by recording adverse events during the study.

**Statistical Methods:** Effectiveness was demonstrated if there was a significant difference between treatment groups with respect to both co-primary variables. For the first co-primary variable, a generalized linear model with cumulative logit link was used to estimate and test the (cumulative) odds ratio of IVP vs. CP utilizing the GLIMMIX procedure of SAS. The model included treatment as a fixed effect and site and treatment-by-site as random effects.

The second co-primary variable was analyzed using a mixed model to estimate and test the mean noise aversion behaviors score utilizing the MIXED procedure of SAS. The model included treatment, time point, and time point-by-treatment interaction as fixed effects, subject, site and site-by-treatment interaction as random effects, and baseline as covariate. The between/within subject covariance was modelled as unstructured.

**Results:** One hundred and ninety-three (193) animals (89 treated and 104 control) were evaluated for effectiveness. For the first co-primary variable of owner assessed overall treatment effect, the proportion of dogs with good or excellent treatment effect was higher in dogs treated with imepitoin (59/89 dogs) than in those administered control product (26/104 dogs). The proportion of dogs with some, no, or worse effect was higher in dogs administered control (78/104 dogs) than in those treated with imepitoin (30/89 dogs).



Analysis of owner assessed overall treatment effect revealed an odds ratio of 5.048 (95% CI (2.64,9.66)) which was substantially larger than 1, indicating difference of imepitoin compared to control with a significant p-value of 0.0001, in favor of imepitoin.

For the second co-primary variable of the owner's scoring for anxious responses in their dogs, the mean sum of behavior scores over the treatment period was significantly different between imepitoin and vehicle control (p-value = 0.0004). The data were taken before treatment start (baseline) and post-treatment at 4 consecutive time points during New Year's Eve. Both treatment groups exhibited a characteristic progression of the level of noise aversion behaviors towards midnight, followed by a gradual decline afterwards.

The overall attenuated level of noise aversion behaviors in the imepitoin group was clearly detectable, also accompanied by a smaller data scatter. The negative estimate for the treatment difference of -6.8 (95%CI (-10.1, -3.5)) indicated that the noise aversion behaviors in the imepitoin treated dogs were reduced compared to the control group, again being significant at a p-value of 0.0004.

**Adverse Reactions:** No serious adverse reactions were reported during the study. The incidence for any nonserious adverse reactions was higher in the imepitoin group (46.5% of dogs with at least one reaction) than in the vehicle control group (12.1% of dogs with at least one reaction). In total, 118 adverse reactions were reported in 53 imepitoin-treated dogs compared to 26 adverse reactions in 15 vehicle control dogs.

The most common adverse reactions correlating to imepitoin treatment were ataxia, increased appetite, lethargy, and emesis. Additionally, hyperactivity, somnolence, aggression, hypersalivation, and anorexia were considered to be highly likely related to treatment with imepitoin.

**Table II.2. Adverse Reactions – Number (%) of dogs**

<b>Adverse Reaction</b>	<b>Imepitoin (n=114)</b>	<b>Vehicle Control (n=124)</b>
Ataxia	39 (34.2)	4 (3.2)
Increased appetite	21 (18.4)	1 (0.8)
Lethargy	13 (11.4)	3 (2.4)
Emesis	9 (7.9)	2 (1.6)
Hyperactivity	7 (6.1)	1 (0.8)
Somnolence	3 (2.6)	1 (0.8)
Aggression	3 (2.6)	0
Hypersalivation	3 (2.6)	0
Anorexia	2 (1.8)	1 (0.8)

Ataxia was the most frequently reported adverse reaction in the imepitoin group beginning in all reported cases on the first day of treatment, in 75.6% of those cases between 30 minutes and 4 hours after drug administration. In 51.2% of the dogs exhibiting ataxia, the signs of ataxia resolved on the day of onset with continued imepitoin treatment, and in 24.4% the signs resolved on the next day. Ataxia led to premature discontinuation of imepitoin treatment in 6 cases. In an additional 11 cases, investigators lowered the dose of imepitoin due to ataxia.

Three adverse reactions were reported as aggression: growling towards a young child, and two cases of seeming disinhibited (lack of restraint or self-control) towards other dogs. Anxiolytic drugs acting at the benzodiazepine receptor site, including imepitoin, may lead to disinhibition of fear-based behaviors and may therefore result in a change in aggression level.

**Conclusions:** The administration of 30 mg/kg body weight imepitoin twice daily starting two days prior to the day of the expected noise event, and continuing through the noise event, was safe and effective for treatment of acute behavior abnormalities associated with noise aversion in dogs.

### III. TARGET ANIMAL SAFETY

The safety of Pexion™ (imepitoin tablets) was demonstrated in one laboratory margin of safety study described below (Study No. 021483//6150-0802-06C-097). During the 6-month study in healthy dogs, there were no test article-related effects seen in ophthalmology examinations, urinalyses, or electrocardiograms (ECGs) for any of the treated groups. Observations related to the test article include signs of sedation (decreased activity, relaxed nictitating membranes, eyelid closure, ataxia, loss of righting reflex, and abnormal postural responses), intermittent tremors, nystagmus, vomiting, salivation, and weight gain. Dose-dependent increases in serum cholesterol and serum creatinine (without corresponding increase in BUN) were observed.

The fed/fasted pharmacokinetic study (Study No. 006-00944 // 6150-0802-06C-143) demonstrated that the systemic exposure to imepitoin was greater for fasted dogs compared to fed dogs. The laboratory safety study was conducted in fasted dogs.

#### A. Six-Month Target Animal Safety Study

**Title:** A six-month oral toxicity study of ELB 138 in Beagle dogs (Study No. 021483//6150-0802-06C-097)

**Study Dates:** September 2007 to December 2008

**Study Location:** Concord OH

**Study Design:**

**Study Objective:** The objective of this study was to assess the toxicity of imepitoin (ELB 138) in dogs when administered orally, twice daily for 6 months. This masked, 6-month oral safety study was conducted in accordance with the Good Laboratory Practice (GLP) regulations.

Study Animals: 32 healthy Beagle dogs, approximately 5.5 months of age and 4.9 to 7.3 kg body weight, 8 dogs per group (4 males and 4 females)

Treatment Groups and Drug Administration: Imepitoin was administered as an oral tablet twice-daily at approximately 12-hour intervals for 6 months (26 consecutive weeks). The actual dose administered to each dog was calculated and adjusted based on the most recent body weight of each dog. Dosing occurred under fasted conditions. Dogs were fed approximately 4 hours following the first dose of the day. The fasting periods prior to the first and second daily dosing were a minimum of 19 and 7 hours, respectively. Vehicle control dogs received a single tablet (scored tablet without imepitoin) orally twice a day.

**Table III.1. Six-month Target Animal Safety Study:**

<b>Dosage Group</b>	<b>Number of Dogs (Males/Females)</b>	<b>Dosage, b.i.d.*</b>	<b>Treatment Duration</b>	<b>Dosage Forms</b>
0X	4/4	0 mg/kg	6 months	Scored tablets without imepitoin
1X	4/4	30 mg/kg	6 months	Scored imepitoin tablets**
3X	4/4	90 mg/kg	6 months	Scored imepitoin tablets**
5X	4/4	150 mg/kg	6 months	Scored imepitoin tablets**

\*b.i.d. = twice daily

\*\*Scored tablets containing 100 or 400 mg of imepitoin per tablet

Measurements and Observations: The dogs were evaluated daily for changes in clinical signs and food consumption and at protocol-specified intervals for physical, neurological and ophthalmologic examination, body weight, complete blood count (CBC), clinical chemistry, coagulation profile, urinalysis, and electrocardiography. At the conclusion of the study, dogs were euthanized and necropsied for pathology and histopathology. Additionally, plasma imepitoin concentrations were obtained at two timepoints during the study (Weeks 4 and 24).

**Statistical Methods**: The endpoints were analyzed by either analysis of variance (bone marrow and organ weights) or repeated measures analysis of covariance (body weights, food consumption, complete blood counts, clinical chemistries, coagulation profile, urinalyses). If the 'treatment' effect was significant ( $p \leq 0.10$ ), linear contrasts were constructed for pair-wise comparison of each active treatment group with the control. All pair-wise comparisons of active treatment groups with the control were tested at the 0.10, 0.05, and 0.01 levels of significance.

**Results**:

Clinical observations: In-life observations, including cage-side observations, detailed clinical observations, physical/neurological observations, and weekly physical observations were conducted at designated intervals during the study. Observations that are considered treatment-related include:

*Neurologic signs:* Signs of sedation: Decreased activity and relaxed nictitating membranes were seen in all groups and increased in frequency as the dose increased. Eyelid closure and ataxia were seen in 5X dogs only. Loss of righting reflex was seen in one 5X dog on one occasion. Abnormal postural response (extensor thrust) was seen in one dog in the 1X group. Other neurologic signs included intermittent tremors and nystagmus each in one dog in the 5X group.

*Gastrointestinal signs:* One dog in the 5X group reportedly became thin and dehydrated. Vomiting and salivation were seen in all groups and had the greatest frequency in the 5X group. White material in the feces occurred in a dose-dependent manner. All dogs in all groups had occasional diarrhea.

Weight gain and food consumption: All groups gained weight over the course of the study. Dogs in the 3X group had the greatest weight gain when compared to other groups after 6 months of treatment. The final body weight, mean cumulative body weight gain, and food consumption were less for dogs in the 5X group when compared to the other groups after 6 months of treatment, suggesting that doses of 5X may delay weight gain in growing animals.

Ophthalmology and electrocardiography (ECG): There were no treatment-related changes in ophthalmologic examinations and ECGs for any of the treated groups compared to the control group.

Clinical pathology:

*CBC:* Most dogs in the 5X group had lower hematocrit and hemoglobin values than dogs in the other groups, but all values stayed within the reference range. A mild increase in mean corpuscular volume (MCV) was seen two 5X dogs. These findings were not associated with any clinical abnormalities.

*Clinical Chemistry:* All dogs in the 3X and 5X groups had dose-dependent elevations in serum creatinine. Dose-dependent elevations in cholesterol occurred in all treated groups. Elevated blood urea nitrogen (BUN) was observed in one control, two 1X, three 3X, and three 5X dogs, but it was not seen in conjunction with elevated creatinine. Most dogs in the 5X group had lower serum albumin values than dogs in the other groups, although values stayed within the reference range. Dogs in the 3X and 5X groups had alkaline phosphatase (ALP) and phosphorus (P) values that decreased slower than expected for the age of the dogs than dogs in the other groups. The ALP increased in one 5X dog. Hyperglobulinemia was seen in three 5X dogs. These findings were not associated with any clinical abnormalities.

*Coagulation profile:* Most dogs in the 5X group had higher activated partial thromboplastin time (APTT) than dogs in the other groups, although values stayed within the reference range.

*Urinalyses:* There were no statistically significant changes in urinalysis parameters for any treated group when compared to the vehicle control group or pretest values.

Organ Pathology/Histopathology: The findings observed for organ weights and gross necropsies were considered to be incidental, spontaneous, and consistent with the age and breed of animals utilized in this study. On histopathology,

proximal renal tubular vacuolization was observed in one control, two 1X, three 3X, and four 5X dogs. Lesions were more diffuse as the dose increased but all lesions were considered minimal to mild. There was no conclusive evidence of renal disease in these dogs. Centrolobular liver vacuolization was observed in two control, five 1X, three 3X, and one 5X dogs.

Pharmacokinetics: Maximum concentrations of imepitoin were typically attained at 2 hours (the first post-dose sampling time), at Weeks 4 and 24. The elimination of half-life values for imepitoin ranged from 1.0 to 3.6 hours at Week 4, and from 1.1 to 5.3 hours at Week 24 (mean values ranged from 1.6 to 2.3 hours at Week 4, and from 1.7 to 2.8 hours at Week 24). The plasma drug levels observed indicate that systemic accumulation of imepitoin occurred during the study.

**Conclusions**: Six months of oral administration of imepitoin tablets to male and female Beagle dogs at a dose of 30 mg/kg body weight twice a day was generally well tolerated. Doses of 90 (3X) and 150 mg/kg body weight (5X) twice a day produced signs of sedation, tremors, and nystagmus mostly at the 5X dose. Dose-dependent salivation, vomiting, and white material in the feces were seen. Dose dependent increases in serum creatinine and cholesterol were seen at the 3X and 5X levels. The pharmacokinetics data from the study indicated that systemic accumulation of imepitoin occurred during the study. The study supports the safe use of imepitoin in dogs when used at the labeled dose and duration.

## **B. Pharmacokinetic Study**

**Title**: Effect of prandial state on pharmacokinetics of ELB 138 in dogs following repeated oral administration (Study No. 006-00944 // 6150-0802-06C-143)

**Study Dates**: March 2007 to April 2008

**Study Location**: Las Cruces, NM

### **Study Design**:

Study Objective: The objective of this study was to investigate the comparative pharmacokinetics (PK) of imepitoin (ELB 138), following repeated oral dosing, when it was administered twice daily to fed or fasted dogs. This study was conducted as a two-way (2x2) crossover design in accordance with the Good Laboratory Practice (GLP) regulations.

Study Animals: 12 healthy Beagles (6 males and 6 females), approximately 2 to 7 years of age and 8.3 to 9.5 kg body weight.

Treatment Groups and Drug Administration: The dogs were randomly assigned to two groups (A and B), each consisting of three males and three females. Imepitoin was administered orally (tablets) at a targeted rate of 30 mg/kg body weight per dose. Actual dosages ranged from 26.6 to 31.3 mg/kg body weight. For each of the two study periods, the drug was given once daily on days 0 and 5, and twice daily on days 1-4. There was a 14-day interval between the two treatment periods.

**Table III.2. Study Design**

<b>Group</b>	<b>No. of Female Dogs</b>	<b>No. of Male Dogs</b>	<b>Prandial State for Period I</b>	<b>Prandial State for Period II</b>
A	3	3	Fasted	Fed
B	3	3	Fed	Fasted

"Fed" dogs were treated with imepitoin approximately 0.5 hours after food was offered. "Fasted" dogs were fasted approximately 7.5 to 8 hours prior to treatment.

Measurements and Observations: Physical examinations were performed on Study Days -1, 6, 19, and 26 to assess the dogs' overall health status and any potential responses to the test article. The dogs were observed once daily for any clinical abnormalities. For dose-calculation purposes, body weights were obtained on Study Days -1, and 19.

Two different blood sampling regimens were employed. On days 0 and 5 of each period, blood for plasma samples was collected prior to dosing (0) and at 0.5, 1, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 8, 12, and 24 hours following dosing. Samples were collected, relative to the morning dosing only, on study days 1-4 of each period at pre-dose (0 hour), 1.75 hour, and 12 hour (immediately prior to the next scheduled dose).

**Statistical Methods:** Data on each of the pharmacokinetic parameters were statistically analyzed via an analysis of variance (ANOVA) procedure appropriate for a two-period crossover design with sex of the dog as a main effect and with repeated measures at study days 0 and 5 included in the ANOVA model in order to evaluate the effect of prandial state and any potential interaction of prandial state with either sex or day. Statistical analyses of the data on several of the PK parameters, in particular,  $C_{max}$  and  $AUC_{last}$ , were based on a natural logarithmic transform in order to better satisfy the statistical assumptions of normality and homoscedasticity.

**Results:**

Clinical observations: Overall, the dogs were healthy throughout the course of the study as evidenced by daily observations, physical examinations, and body weights.

Pharmacokinetics: Least squares means and geometric means for selected PK parameters are presented in Table III.3.  $AUC_{last}$  is not shown because its values are similar to  $AUC_{inf}$ .

**Table III.3. Least squares means and geometric means† for selected PK parameters<sup>a</sup>**

<b>Effect</b>	<b>T<sub>max</sub> (hr)</b>	<b>t<sub>1/2</sub>* (hr)</b>	<b>C<sub>max</sub>† (ng/ml)</b>	<b>AUC<sub>inf</sub>† (hr*ng/ml)</b>	<b>Vz† (ml/kg)</b>	<b>Cl† (ml/hr/kg)</b>
Fasted	2.17	1.47	17168	90310	663	320
Fed	2.02	1.95	14892	69238	1129	417
Day 0	2.44	1.75	17190	101407	704	285
Day 5	1.75	1.66	14873	61661	1062	468

<sup>a</sup>Pairs of means in bold differ significantly (p≤0.05).

\*HL Lambda z

†Geometric means

T<sub>max</sub>=time to maximum plasma concentration

t<sub>1/2</sub>=terminal half life

C<sub>max</sub>=maximum plasma concentration

AUC<sub>inf</sub>=area-under-the-concentration-time-curve

Vz=volume of distribution

Cl=total body clearance

The main effect of prandial state was significant (p<0.03) for t<sub>1/2</sub>, AUC<sub>inf</sub>, Vz, and Cl. In fasted dogs, t<sub>1/2</sub>, Vz, and Cl were less compared to fed dogs. As indicated by the areas under the time-concentration curves, fasted dogs were exposed to 20% greater imepitoin than were fed dogs. Although C<sub>max</sub> was 15% greater for fasted dogs, this difference was not significant (p>0.15).

The effect of day was significant (p<0.03) for several factors, including T<sub>max</sub>, mean residence time (MRT<sub>inf</sub>), AUC<sub>inf</sub>, Vz, and Cl. AUC<sub>inf</sub> at day 5 was 40% less than at day 0. This effect was independent of prandial state.

**Conclusions:** Following an oral dose of 30 mg/kg body weight, maximum concentrations of imepitoin were achieved at approximately 2 hours. Imepitoin was eliminated with a half-life from approximately 1.5 to 2 hours. A prandial effect was noted wherein fasted dogs had approximately 20% greater systemic exposure than dogs that were fed prior to dosing.

#### **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 approval of this NADA.

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

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

Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans

## **VI. AGENCY CONCLUSIONS**

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Pexion™, when used according to the label, is safe and effective for the treatment of noise aversion in dogs.

### **A. Marketing Status**

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to assess the health of the dog to determine if imepitoin is an appropriate treatment, and to monitor the safe use of the product, including treatment of any adverse reactions.

### **B. Exclusivity**

Pexion™, as approved in our approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) because this is the first time we are approving this active ingredient in a new animal drug application under section 512(b)(1) of the FD&C Act.

### **C. Patent Information:**

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.