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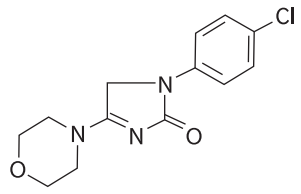
Pexion™
(imepitoin tablets)
For oral use in dogs only

Boehringer Ingelheim

Caution:
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description:
PEXION (imepitoin tablets) acts as a low affinity partial agonist on the $GABA_A$ receptor by increasing the affinity that GABA has for its receptor site, thus facilitating the opening of the GABA-activated Cl^- channel leading to postsynaptic inhibition. The chemical name of imepitoin is 1-(4-Chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1 H-imidazol-2-one. The structural formula of imepitoin is:



Indication:
PEXION tablets are indicated for treatment of noise aversion in dogs.

Dosage and Administration:
Always provide the Client Information Sheet with each prescription.

PEXION should be administered orally at a dose of 13.6 mg imepitoin per lb body weight (30 mg/kg) twice daily, approximately 12 hours apart using a suitable combination of whole and half tablets as detailed in Table 1. Initiate therapy starting 2 days prior to the day of the expected noise event and continuing through the noise event.

Table 1 - Number of tablets (to be given twice daily)

Dose: 13.6 mg/lb (30 mg/kg) (twice daily)	Number of tablets per administration	
Bodyweight in lbs (kg)	100 mg tablet	400 mg tablet
4.4 – 6.5 (2.0 – 2.9)	½	
6.6 – 8.7 (3.0 – 3.9)	1	
8.8 – 13.1 (4.0 – 5.9)	1 ½	
13.2 – 21.9 (6.0 – 9.9)		½
22.0 – 35.2 (10.0 - 15.9)		1
35.3 – 50.6 (16.0 – 22.9)		1 ½
50.7 – 66.0 (23.0 – 29.9)		2
66.1 – 81.5 (30.0 – 36.9)		2 ½
81.6 – 96.9 (37.0 – 43.9)		3
97.0 – 110.1 (44.0 – 49.9)		3 ½
110.2 – 123.2 (50.0 – 55.9)		4
Over 123.2 (Over 55.9)		4 ½

Contraindications:
PEXION should not be given to dogs with hypersensitivity to imepitoin.

Human Warnings:
Not for human use. Keep out of reach of children. Consult a physician in case of accidental ingestion by humans.

Precautions:
The safe use of PEXION has not been evaluated in dogs younger than 5 months of age or in dogs with severely impaired hepatic, renal or cardiovascular function. PEXION is metabolized by the liver.

The safe use of PEXION in breeding, pregnant, or lactating dogs has not been evaluated.

PEXION has not been evaluated for aversion behaviors to thunderstorms.

Anxiolytic drugs acting at the benzodiazepine receptor site, including imepitoin, may lead to disinhibition (lack of restraint or self-control) of fear-based behaviors and may therefore result in a change in aggression level. Careful observation by the owners is recommended during treatment.

Adverse Reactions:
In a well-controlled field study, in which a total of 238 dogs ranging from 1 to 14 years of age and representing both mixed and pure breed dogs were treated (114 treated with 30 mg/kg imepitoin twice daily and 124 treated with control twice daily), no serious adverse reactions were observed.

Table 2 shows the number of dogs displaying adverse reactions possibly related to treatment (some dogs experienced more than one adverse reaction).

Table 2 - Adverse Reactions - Number (%) of dogs

Adverse Reaction	Imepitoin n=114	Placebo n=124
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 most cases between 30 minutes and 4 hours after initial dose administration.

In 51.2% of affected dogs, the signs of ataxia resolved on the day of onset with continued treatment, and in 24.4% on the next day. Ataxia led to premature discontinuation of imepitoin treatment in six cases. In an additional 11 cases, investigators lowered the dose of imepitoin due to ataxia.

Anxiolytic drugs acting at the benzodiazepine receptor site, including imepitoin, may lead to disinhibition (lack of restraint or self-control) of fear-based behaviors and may therefore result in a change in aggression level. Three adverse reactions were reported as aggression in the imepitoin group, including growling towards a young child and disinhibition towards other dogs. Careful observation by the owners is recommended during treatment.

To report suspected adverse reactions, to obtain a Safety Data Sheet, or for technical assistance, call Boehringer Ingelheim at 1-888-637-4251.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

Information for Dog Owners:
Always provide the Client Information Sheet with each prescription and review it with the dog owner. Advise dog owners that adverse reactions can occur with use of PEXION. The most common adverse reactions reported during the field study included ataxia, increased appetite, lethargy (lack of energy), and vomiting. Advise dog owners that PEXION may lead to disinhibition (lack of restraint or self-control) of fear-based behaviors and may therefore result in a change in aggression level. Careful observation by the owners is recommended during treatment.

Clinical Pharmacology:
Utilizing a two-way crossover design, a multiple-dose study was conducted with 12 dogs (6 males and 6 females) to evaluate the effect of prandial state on the pharmacokinetics of imepitoin administered orally by tablets. Mean PK

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Client Information Sheet

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The Client Information Sheet contains important information about PEXION. You should read this information before you start giving PEXION and review it each time the prescription is refilled as there may be new information. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk with your veterinarian if you do not understand any of this information or if you want to know more about PEXION.

What is PEXION?
PEXION (imepitoin tablets) is used to treat noise aversion in dogs.

What is Noise Aversion?
Dogs with noise aversion are sensitive to loud noises such as fireworks, street/traffic noises, gun shots, etc. which may cause them to exhibit signs of fear and anxiety.

Typical signs of anxiety and fear associated with noise aversion include:
- Panting,
- Shaking/trembling,
- Cowering,
- Barking/whining/howling,
- Restlessness/pacing,
- Increased vigilance,
- Owner seeking behavior,
- Hiding,
- Running around/bolting/destructiveness,
- Self-harm,
- Freezing in place behavior,
- Inappropriate urination/defecation/diarrhea,
- Vomiting/drooling saliva.

What should I tell my veterinarian about my dog before starting PEXION?
- Tell your veterinarian about other medications your pet is taking, including prescription drugs, over the counter drugs, heartworm preventatives, flea & tick medications, and vitamins and supplements, including herbal medications.
- Tell your veterinarian if your dog is pregnant, nursing, or you intend to breed him/her.
- Tell your veterinarian if your dog has any other serious health conditions, including impaired hepatic (liver), renal (kidney), or cardiovascular (heart) function.
- Tell your veterinarian if your dog has a history of aggressive behavior.

Talk to your veterinarian about:
- The risks and benefits of giving PEXION to your dog

Which dogs should not take PEXION?
The safe use of PEXION has not been evaluated in dogs
- Younger than 5 months of age
- With severely impaired liver, kidney, or heart function
- Breeding, pregnant, or nursing

What are some of the possible side effects of PEXION?
Like all drugs, PEXION may cause side effects, even at the prescribed dose. Contact your veterinarian immediately if your dog develops a serious or concerning medical problem or side effect while taking PEXION.

The most common side effect with PEXION is ataxia, which means your dog may appear wobbly or not in control of its body movements. In most dogs, ataxia lessens or goes away by the next day with continued treatment.

parameters of interest are indicated in Table 3. Total systemic exposure to imepitoin, as indicated by area-under-the-concentration-time curve (AUC_{inf}), was 20% greater for the fasted dogs.

Table 3 - Least squares means and geometric means† for selected PK parameters[a]

Effect	T_{max} (hr)	$T_{½}^{*}$ (hr)	C_{max}† (ng/mL)	Auc_{inf}† (hr*ng/mL)	Vz† (mL/kg)	Cl† (mL/hr/kg)
Fasted	2.17	**1.47**	17168	**90310**	**663**	**320**
Fed	2.02	**1.95**	14892	**69238**	**1129**	**417**

*HL Lambda z.

†Geometric means

[a]Pairs of means in bold differ significantly ($p \leq 0.05$)

T_{max}= time to maximum plasma concentration

$t_{1/2}$= terminal half life

C_{max}= maximum plasma concentration

AUC_{inf} = area-under-the-concentration-time-curve

Vz = volume of distribution

Cl = total body clearance

Plasma imepitoin concentrations were determined on two occasions during the 6-month target animal safety study (See **Animal Safety**). Maximum concentrations of imepitoin were typically attained at 2 hours, the first post-dose sampling time, at Weeks 4 and 24. The elimination 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.

Effectiveness:
PEXION (imepitoin tablets) was evaluated in a European randomized multi-center, double-blind, vehicle-controlled field study. Effectiveness was evaluated in client-owned dogs ranging in age between 1 and 14 years, and in body weight between 3 and 72 kg. A total of 251 dogs were randomized, 193 of which were eligible (at least one dose of medication and data for evaluation of co-primary endpoints) for evaluation of effectiveness: 89 dogs received 30 mg/kg imepitoin twice daily and 104 dogs received the vehicle control twice daily for three days (the two days prior to New Year's Eve and continuing on the day of the noise event). All dogs had previously demonstrated noise aversion behaviors due to fireworks as documented by their owners.

The first co-primary endpoint was 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 treatment effect was higher in dogs administered control (78/104 dogs) than in those treated with imepitoin (30/89 dogs). The difference was statistically significant (Odds Ratio =5.048; p=0.0001, 95% CI [2.64; 9.66]). The second co-primary variable was the owner's scoring for noise aversion behavior responses in their dogs. Owner-reported measures of the 16-item noise aversion behavior symptoms were derived from the Lincoln Sound Sensitivity Scale* (such as running around, hiding, restlessness/pacing, panting, shaking or trembling) of the dog during a noise event. The mean sum of behavior scores over the treatment period was significantly different between imepitoin and 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 noise aversion behaviors towards midnight, followed by a gradual decline afterwards. Overall, the noise aversion behaviors in the imepitoin group were clearly attenuated and the negative estimate for the treatment difference of -6.8 (95% CI [10.1; -3.5]) indicated that the noise aversion behavior level in the imepitoin group was reduced compared to controls (p = 0.0004).

Animal Safety:
In a 6-month target animal safety study, PEXION tablets were administered to 32 healthy beagle dogs, 8 per treatment group, approximately 5.5 months of age, at 0, 1, 3, and 5 times the maximum recommended dosage (0, 30, 90, and 150 mg/kg twice daily). Clinical abnormalities seen during the study that are treatment-related include signs of sedation (decreased activity, relaxed nictitating membranes, eyelid closure, ataxia, loss of righting reflex, and abnormal postural responses), intermittent tremors, and nystagmus. Gastrointestinal signs (vomiting and salivation) were also seen. One dog at the highest dosage (5X) became thin and dehydrated over the course of the study. White material was seen in the feces in a dose-dependent manner.

Dogs in the 3X group had the greatest weight gain and dogs in the 5X group had reduced weight gain and food consumption when compared to other groups after 6 months of treatment.

Dose-dependent hypercholesterolemia was seen in the 3X and 5X dogs. Dose-dependent creatinine elevation without corresponding increase in BUN was seen in all 3X and 5X dogs. Histopathological findings included centrolobular liver vacuolization and dose-dependent proximal renal tubular vacuolization.

There were no treatment-related changes in ophthalmologic examinations, urinalyses, or electrocardiograms (ECGs) for any of the treated groups.

Storage Information:
Store at 20° to 25°C (68° to 77°F), excursions permitted between 15° and 30°C (between 59° and 86°F).

How Supplied:
PEXION (imepitoin tablets) is supplied as white single-scored oblong tablets in strengths of 100 mg and 400 mg.
NDC 0010-4484-02 - 100 mg, 30 tablets

NDC 0010-4485-02 - 400 mg, 30 tablets

Approved by FDA under NADA # 141-509

References:
*Mills DS, Braem Dube M, Zulch H. Stress and Pheromonatherapy in Small Animal Clinical Behaviour. 1 ed. Chichester: Wiley-Blackwell; 2013, pp. 191-214 and 259-263.

Marketed by:
Boehringer Ingelheim
Animal Health USA Inc.
Duluth, GA 30096

Made in Germany

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Contact your veterinarian if you are concerned about your dog's level of ataxia or if the ataxia worsens with continued treatment.

Other common side effects with PEXION include increased appetite, lethargy (lack of energy), and vomiting. There are other side effects which may occur. For a complete list, ask your veterinarian.

Drugs used to treat anxiety, like PEXION, may lead to disinhibition (lack of restraint or self-control) of fear-based behaviors and may therefore result in a change in aggression level. Dogs should be carefully watched during treatment. Contact your veterinarian if you are concerned about your dog's behavior.

To report a suspected adverse reaction (side effects) contact Boehringer Ingelheim at 1-888-637-4251.

How do I give PEXION to my dog and what should I expect after administration?
PEXION should be given to your dog in their mouth (orally) twice a day, about 12 hours apart.

PEXION should be started 2 days before the day of the expected noise event and continued through the noise event. For example: If you are planning to attend a celebration with fireworks on Saturday, you would need to begin giving PEXION to your dog on Thursday, twice each day, until the fireworks celebration has ended. Any questions about the duration of treatment should be discussed with your veterinarian.

If needed, PEXION tablets can be hidden in a small amount of food before placing directly into your dog's mouth. The tablets should not be crushed or placed into the dog's food bowl.

Follow your veterinarian's instructions for how much PEXION to give your dog.

If your dog vomits within 15 minutes of giving PEXION, your dog can be given the same number of tablets again. If your dog vomits more than 15 minutes after giving PEXION, do not give PEXION again until the next scheduled dose.

The onset of action varies between individuals, and starts between a couple of hours and 2 days of treatment.

Most side effects, especially ataxia (wobbly gait), start within the first 4 hours after administering the dog's first PEXION tablet(s), and resolve with continuation of treatment within 12 – 48 hours.

What if my dog receives more PEXION tablets than what is prescribed?
Contact your veterinarian immediately.

What else should I know about PEXION?
PEXION is not for use in humans.

You should keep PEXION in a secure storage area out of the reach of children, as well as dogs, cats and other animals to prevent accidental ingestion or overdose.

If PEXION is accidentally ingested, contact a physician. It is important to show the treating physician a copy of the package insert, label, or client information sheet. PEXION is a $GABA_A$ receptor partial agonist.

This client information sheet contains a summary of important information about PEXION. For more detailed information about PEXION, talk with your veterinarian.

Storage Statement:
PEXION (imepitoin tablets) can be stored at room temperatures between 68°F to 77°F. Temperatures as low as 59°F and as high as 86°F can be acceptable for short periods of time.

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