1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Pexion 100 mg tablets for dogs
Pexion 400 mg tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains:

Active substance:
Imepitoin 100 mg
Imepitoin 400 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, oblong, half-scored tablets with embedded logo “I 01” (100 mg) or “I 02” (400 mg) on one side.
The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

For the reduction of the frequency of generalised seizures due to idiopathic epilepsy in dogs for use after careful evaluation of alternative treatment options.
For the reduction of anxiety and fear associated with noise phobia in dogs.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in dogs with severely impaired hepatic function, severe renal or severe cardiovascular disorders.

4.4 Special warnings for each target species

Idiopathic epilepsy
The pharmacological response to imepitoin may vary and efficacy may not be complete. On treatment, some dogs will be free of seizures, in other dogs a reduction of the number of seizures will be observed, whilst others will be non-responders. For this reason, careful consideration should be given before deciding to switch a stabilized dog onto imepitoin from a different treatment. In non-responders, an increase in seizure frequency may be observed. Should seizures not be adequately controlled, further diagnostic measures and other antiepileptic treatment should be considered. When transition between different antiepileptic therapies is medically required, this should be done gradually and with appropriate clinical supervision.

The efficacy of the veterinary medicinal product in dogs with status epilepticus and cluster seizures has not been investigated. Therefore, imepitoin should not be used as primary treatment in dogs with cluster seizures and status epilepticus.

No loss of anticonvulsant efficacy (tolerance development) during continuous treatment of 4 weeks was observed in experimental studies lasting 4 weeks.

No definitive conclusions can be drawn on the effectiveness of imepitoin as an add-on therapy to phenobarbital, potassium bromide and/or levetiracetam from the limited studies available (see section 4.8).

Noise phobia
Efficacy for reduction of anxiety and fear associated with noise phobia has not been tested in dogs younger than 12 months.

Up to 2 days of pre-treatment may be necessary to achieve optimal anxiolytic efficacy in dogs with noise phobia. See section 4.9 (amounts to be administered and administration route).

4.5 Special precautions for use

Special precautions for use in animals
The safety of the veterinary medicinal product has not been tested in dogs weighing less than 2 kg or in dogs with safety concerns such as renal, liver, cardiac, gastrointestinal or other disease.

Anxiolytic drugs acting at the benzodiazepine receptor site, such as imepitoin, may lead to disinhibition of fear-based behaviours. The product may therefore result in an increase or decrease in aggression levels.
In dogs with a history of aggression problems, a careful benefit-risk evaluation should be made prior to treatment. This evaluation may include consideration of inciting factors or situations associated with previous aggressive episodes. Prior to initiating treatment in these cases, behaviour therapy or referral to a behaviour specialist should be considered. In these dogs, additional measures to mitigate the risk of aggression problems should be implemented as appropriate before treatment is initiated.

Mild behavioural or muscular signs may be observed in dogs upon abrupt termination of treatment with imepitoin.

The claim for the treatment of noise phobia is based on a pivotal field study which investigated a 3 day course of treatment for a noise event associated with fireworks. Longer treatment durations for noise phobia should be at the benefit-risk assessment of the veterinarian. Consideration should be given to use of a behavioural modification programme.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Ingestion of this product may cause dizziness, lethargy and nausea. In case of accidental ingestion especially by a child, seek medical advice immediately and show the package leaflet or the label to the physician.
To prevent accidental ingestion of tablets, the cap of the bottle should be replaced immediately after withdrawing the required number of tablets for one administration.

4.6 Adverse reactions (frequency and seriousness)

Idiopathic epilepsy
The following mild and generally transient adverse reactions have been observed in pre-clinical and clinical studies for the epilepsy claim in order of decreasing frequency: ataxia, emesis, polyphagia at the beginning of treatment, somnolence (very common); hyperactivity, apathy, polydipsia, diarrhoea, disorientation, anorexia, hypersalivation, polyuria (common); prolapsed nictitating membrane and decreased sight (isolated reports).

In epileptic dogs, aggression has been uncommonly reported, and increased sensitivity to sound and anxiety have been rarely reported in the field. These signs are potentially treatment related. They may also be present during the preictal or postictal period or as behaviour changes which occur as part of the disease itself.

A mild elevation in plasma creatinine, urea and cholesterol levels has been observed in dogs treated with imepitoin; however these generally did not exceed the normal reference ranges and were not associated with any clinically significant observations or events.

Noise phobia
The following adverse reactions have been observed during preclinical and clinical studies conducted to support the noise phobia claim: ataxia, increased appetite, lethargy (very common); emesis, aggression (see section 4.5) (common); hyperactivity, somnolence, hypersalivation (uncommon). Most events are transient, resolving during or shortly after the end of the treatment course.

Transient ataxia was reported very commonly during a clinical trial for noise phobia and occurred early in the treatment course. In more than half of the dogs that experienced ataxia during this clinical trial the signs resolved spontaneously within 24 hours in spite of continued treatment and in half of the remaining dogs within 48 hours.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reactions)
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The use of the veterinary medicinal product is not recommended in male breeding dogs or in female dogs during pregnancy and lactation (see section 4.10).

4.8 Interaction with other medicinal products and other forms of interaction

The product has been used in combination with phenobarbital, potassium bromide and/or in a small number of cases with levetiracetam and no harmful clinical interactions were observed (see section 4.4).

4.9 Amounts to be administered and administration route

Idiopathic epilepsy
Oral administration at a dose range of 10 mg to 30 mg imepitoin per kg bodyweight twice daily, approximately 12 hours apart. Each tablet can be halved for appropriate dosing according to the individual bodyweight of the dog. Any remaining half-tablet should be used for the next dose.

The required dose will vary between dogs and will depend on the severity of the disorder.
The recommended initial dose of imepitoin is 10 mg per kg bodyweight twice daily.

Initiate therapy using the bodyweight in kg and the dosing table. If seizures are not adequately reduced following a minimum of 1 week of treatment at the current dose the supervising veterinary surgeon should re-assess the dog. Assuming that the veterinary medicinal product is well tolerated by the dog, the dose can be increased by 50 to 100% increments up to a maximum dosage of 30 mg per kg administered twice daily.

Bioavailability is greater when administered to fasted dogs. The timing of tablet administration in relation to feeding should be kept consistent.

Number of tablets (to be given twice daily) for initiation of epilepsy treatment:

Dose: 10 mg/kg twice daily	Number of tablets per administration	
Bodyweight (kg)	100 mg tablet	400 mg tablet
5	½	
5.1–10	1	
10.1–15	1 ½	
15.1–20		½
20.1–40		1
40.1–60		1 ½
Over 60		2

Noise phobia
Oral administration at a dose of 30 mg imepitoin per kg bodyweight twice daily, approximately 12 hours apart.
Each tablet can be halved for appropriate dosing according to the individual bodyweight of the dog.

Initiate therapy 2 days prior to the day of the expected noise event and continue through the noise event using the bodyweight in kg and the dosing table below.

Bioavailability is greater when administered to fasted dogs. The timing of tablet administration in relation to feeding should be kept consistent.

Number of tablets (to be given twice daily) for noise phobia treatment:

Dose: 30 mg/kg twice daily	Number of tablets per administration	
Bodyweight (kg)	100 mg tablet	400 mg tablet
2.5 – 3.9	1	
4 – 5.9	1 ½	
6 – 7.9	2	
8 – 10.9	3	
11 – 15.9		1
16 – 22.9		1 ½
23 – 29.9		2
30 – 36.9		2 ½
37 – 43.9		3
44 – 49.9		3 ½
50 – 55.9		4
56 – 71.9		4 ½
72 – 80		5

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

In case of repeated overdose of up to 5 times the highest recommended dose of 30 mg imepitoin per kg bodyweight, central nervous system (CNS) effects, gastrointestinal-related effects and reversible prolongation of the QT interval have been noted. At such doses, the symptoms are not usually life-threatening and generally resolve within 24 hours if symptomatic treatment is given.

These CNS effects may include loss of righting reflex, decreased activity, eyelid closure, lacrimation,

dry eye and nystagmus.

At 5 times the recommended dose, decreased bodyweight may be observed.

In male dogs administered 10 times the upper recommended therapeutic dose, diffuse atrophy of seminiferous tubules in the testes and associated decreased sperm counts were seen.
See also section 4.7.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antiepileptics, Other antiepileptics, imepitoin
ATCvet code: QN03AX90

5.1 Pharmacodynamic properties

Imepitoin is a centrally acting substance with anxiolytic and antiepileptic properties which crosses the blood brain barrier without involvement of active transport or active clearance, resulting in immediate equilibrium between plasma and brain. Here it acts as a low affinity partial agonist of the benzodiazepine receptor.

The anxiolytic effect of imepitoin is mediated via the $GABA_A$ receptor. Imepitoin also inhibits seizures via potentiation of the $GABA_A$ receptor-mediated inhibitory effects on the neurons and in addition, imepitoin has a weak calcium channel blocking effect which may contribute to its anticonvulsive properties.

Clinical trials in epilepsy
In a European field trial that compared the efficacy of imepitoin to phenobarbital in 226 dogs with newly diagnosed idiopathic epilepsy, 45% of cases from the imepitoin group and 20% from the phenobarbital group were excluded from the efficacy analysis for reasons that included failure to respond to treatment. In the remaining dogs (64 dogs for Pexion and 88 dogs for phenobarbital), the following clinical results were observed: Mean frequency of generalised seizures was reduced from 2.3 seizures per month in the imepitoin group and from 2.4 seizures per month in the phenobarbital group to 1.1 seizures per month in both groups after 20 weeks of treatment. The difference between imepitoin and phenobarbital groups in the seizure frequency per month after treatment (adjusted for baseline difference) was 0.004, 95% CI [-0.928, 0.935]. During the evaluation phase of 12 weeks, the proportion of generalised seizure-free dogs was 47% (30 dogs) in the imepitoin group and 58% (51 dogs) in the phenobarbital group.

The safety of both treatments was evaluated in the full analysis data set (or safety data set, i.e. 116 animals in the imepitoin group and 110 animals in the phenobarbital group). Increasing doses of phenobarbital were associated with increasing levels of the liver enzymes ALT, AP, AST, GGT, and GLDH. In comparison, none of the five enzymes increased with increasing doses of imepitoin. A slight increase in creatinine values compared to baseline was observed in the imepitoin-treated dogs. However, the upper limit of the confidence interval for creatinine remained within the reference range at all visits. Additionally, fewer adverse events were noted for polyuria (10% vs 19% of dogs), polydipsia (14% vs 23%) and marked sedation (14% vs 25 %) when comparing imepitoin to phenobarbital. Please refer to section 4.6 of the SPC for further details of adverse reactions.

In a US field trial that compared the efficacy of imepitoin at a fixed dose of 30 mg/kg twice daily to a placebo in 151 dogs with idiopathic epilepsy during a treatment period of 84 days, the proportion of generalized seizure-free dogs was 21% (21 dogs out of 99; 95 % CI [0.131; 0.293])

in the imepitoin group and 8% (4 dogs out of 52; 95% CI [0.004; 0.149]) in the placebo group. 25% of dogs did not respond to the treatment with imepitoin (same or increased frequency of seizures).

Clinical trial in noise phobia
In a placebo-controlled field trial with a treatment duration of 3 days, the efficacy of imepitoin was investigated in dogs diagnosed with noise phobia during the traditional New Year's Eve fireworks. For the efficacy analysis, 226 dogs (104 imepitoin, 122 placebo) were eligible (at least one dose of medication & data for evaluation of co-primary endpoints), and the following results were observed for the two co-primary endpoints:

1. Owner assessed overall effect of study treatment (based on signs during a noise event and a comparison to signs during a previous noise event(s) without treatment: The cumulative odds of a good or excellent effect were significantly greater in the imepitoin group compared with the placebo group (Odds Ratio = 4.689; $p < 0.0001$, 95% CI [2.79;7.89]).
2. Owner-reported measure of their dog's anxiety symptoms (based on Lincoln Sound Sensitivity Scale) during a noise event: The sum scores showed a statistically significant treatment effect favouring imepitoin with a difference in anxiety score between imepitoin and placebo of -6.1; $p < 0.0001$, 95% CI [-8.6;-3.6].

5.2 Pharmacokinetic particulars

Absorption
Pharmacokinetic studies indicate that imepitoin is well absorbed (> 92%) after oral administration and that no pronounced first pass effect occurs. After oral administration of imepitoin tablets at 30 mg/kg without food, peak blood concentrations are attained rapidly with a T_{max} of around 2 hours, a C_{max} of about 18 µg/ml. Co-administration of imepitoin tablets with food, reduces the total AUC by 30% but produces no significant change in T_{max} and C_{max}. Gender-specific differences do not occur.

Distribution
Dose linearity occurs over the therapeutic dose range of imepitoin.
Imepitoin has a relatively high volume of distribution (579 to 1548 ml/kg). The *in-vivo* plasma protein binding of imepitoin in dogs is low (60 to 70%). No interaction with highly protein bound compounds is therefore expected. No accumulation of imepitoin in plasma occurs after repeated administration, once steady state is reached.

Metabolism
Imepitoin is extensively metabolised prior to elimination. Metabolite profiles in urine and faeces revealed four major inactive metabolites which are formed by oxidative modification.

Elimination
Imepitoin is rapidly cleared from blood (Cl = 260 to 568 ml/hours/kg) with an elimination half-life of approximately 1.5 to 2 hours. The majority of imepitoin and its metabolites are excreted via the faecal route rather than the urinary route so that no major change in pharmacokinetics and no accumulation is expected in renally impaired dogs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose microcrystalline
Hypromellose
Magnesium stearate
Sodium starch glycolate

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

6.4 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Pack sizes of high-density polyethylene bottle each containing 30, 100 or 250 tablets with a child resistant closure.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Vetmedica GmbH
55216 Ingelheim/Rhein
GERMANY

8. MARKETING AUTHORISATION NUMBERS

EU/2/12/147/001 100 tablets (100 mg)
EU/2/12/147/002 250 tablets (100 mg)
EU/2/12/147/003 100 tablets (400 mg)
EU/2/12/147/004 250 tablets (400 mg)
EU/2/12/147/005 30 tablets (400 mg)
EU/2/12/147/006 30 tablets (100 mg)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25.02.2013
Date of last renewal: 21.11.2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.