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Committee for Medicinal Products for Veterinary Use

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CVMP assessment report for a grouped type II variation for Pexion (EMEA/V/C/002543/II/0011/G)

International non-proprietary name: imepitoin

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Introduction

1.1. Submission of the variation application

In accordance with Article 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Boehringer Ingelheim Vetmedica GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 22 September 2017 an application for a grouped type II variation for Pexion.

1.2. Scope of the variation

Variations requested		**Type**
B.II.e.2.z	Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation	IB
B.II.e.5.a.2	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	IB
B.II.e.5.a.2	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	IB
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The proposed variation is to add a new therapeutic indication: 'For the reduction of anxiety and fear associated with noise phobia in dogs'. The grouped variation is also to add a new pack-size of 30 tablets for Pexion 100 mg tablets and for Pexion 400 mg tablets and to additionally introduce changes in the specification parameters of the immediate packaging. In the framework of this variation, product information is being aligned with QRD template v. 8.1 and changes are implemented following the renewal procedure (EMEA/V/C/002543/R/0010), a type IB variation (EMEA/V/C/002543/IB/0012) and the assessment of the 7th PSUR.

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 2 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

2.1. Quality

2.1.1. Change in the specification parameters and/or limits of the immediate packaging of the finished product

For both tablet sizes (100 and 400 mg), it is proposed that corrections be made to the stated dimensions of the containers and closures. This is due to errors in the originally-submitted documentation. The applicant has confirmed that the bottles and their closures are unchanged from those previously approved. This is considered acceptable.

A "Function test" has been added to the specification for the container and the section "Compliance with food regulation" in the description has been corrected.

2.1.2. Change in pack size of the finished product (400 mg tablets)

This change proposes a 30-tablet presentation for the 400 mg tablet. The 35 ml-container to be used is that currently used for the 100 tablet presentation of the 100 mg tablet. Since this container is already approved for Pexion 100 mg tablets, no additional data are required. An acceptable protocol is provided for post-authorisation stability testing for the first three production batches and one production batch per year thereafter. It should be noted that Pexion tablets have previously been shown to have good stability in unopened and part-used packs.

2.1.3. Change in pack size of the finished product (100 mg tablets)

This change proposes a 30-tablet presentation for the 100 mg tablet. The 15 ml-container to be used is not currently used for Pexion. The specification and description of the container are comparable with those discussed above and are satisfactory. The materials of construction are not described but it is noted that the same identification tests are to be applied as with the larger packs and it can be concluded that the pack will be suitable. An acceptable protocol is provided for post-authorisation stability testing for the first three production batches and one production batch per year thereafter. As noted above, Pexion tablets have previously been shown to have good stability in unopened and part-used packs and there is no reason to suspect that the 30-tablet presentation in the 15 ml-container will be any different.

During the assessment of the current grouped variation, a type IB variation (EMEA/V/C/002543/IB/0012) concerning the deletion of the in-use shelf life for the finished product from the product information was approved; this deletion is reflected in the outcome of the present type II grouped variation (EMEA/V/C/002543/II/0011/G).

Quality-related changes to the SPC/PL are minor and acceptable.

2.2. Safety

The purpose of the variation application is to include a new indication for the product and alter the pack size for the 100 and 400 mg tablets. No new safety data have been provided.

It is considered that the addition of the new indication will not alter the risk to the user or the environment and that the risk mitigation measures accepted for the product are still appropriate. The claimed dosage for the new indication corresponds to the maximum dose recommended for the existing indication of epilepsy. Schemes of treatment are similar for both indications.

The introduction of the smaller pack size of 30 tablets is also acceptable and considered a benefit when the product enters the home as less product is available for accidental exposure.

As part of the recent renewal procedure (EMEA/V/C/002543/R/0010), the requested 'A' phrase, 'Ingestion of this product may cause dizziness, lethargy and nausea', has been included in the product information to inform the user of the concerned risk following accidental ingestion.

2.3. Efficacy

The discussion under *Efficacy* concerns the variation to add a new therapeutic indication: **'for the reduction of anxiety and fear associated with noise phobia in dogs'**.

Fear and anxiety associated with exposure to noises is a common problem in the dog and represents a genuine welfare concern. One study suggests as many as 50% of dogs may be affected by noise phobia. Imepitoin is a partial agonist at the benzodiazepine receptor; activity at the $GABA_A$-receptor mediates its anxiolytic effects.

2.3.1. Pharmacodynamics

The anxiolytic pharmacodynamic properties of imepitoin are supported by the results of eleven pre-clinical studies. In one *in vitro* study, imepitoin is shown to control corticotrophin releasing factor induced activity of neurones in the *locus coeruleus*. Furthermore, nine *in vivo* studies support the presence of anxiolytic effects in both rats and mice after oral or intraperitoneal administration of imepitoin, although the presence and significance of these effects varied between studies. A range of pre-clinical models have been used for the evaluation of the anxiolytic activity of imepitoin; these are based on standard models used for the evaluation of anxiolytic efficacy. In general, the effects of imepitoin were compared *in vivo* with diazepam during the pre-clinical studies submitted. Across these studies, diazepam exerted greater or more consistent anxiolytic effects than imepitoin and a dose dependent anxiolytic response was often observed with diazepam. In comparison, doses of 1 mg/kg imepitoin generally were insufficient to exert an anxiolytic effect, and there was no consistent dose-dependent response observed at higher doses. During these preclinical studies, sedative side effects were only observed in rodents administered higher doses of imepitoin (30 to 200 mg/kg). This was in contrast to rodents administered diazepam (at doses of 3 to 10 mg/kg) in which sedation and/or muscle relaxation were often observed.

A company sponsored pre-clinical study investigated the effects of imepitoin at a planned dose of 20 mg/kg *per os* twice daily for 21 consecutive days in four Beagles with anxiety (Ethier, 2009). Standardised open field tests (interactions with humans, thunder and a Verikennel) commencing one week after the start of imepitoin administration provide some support for an anxiolytic efficacy in the dog (particularly during the human interaction test). The study was underpowered to demonstrate statistical differences.

Overall, the mode of action and anxiolytic pharmacodynamic effects of imepitoin have been sufficiently well characterised in model species.

2.3.2. Pharmacokinetics

The applicant has proposed a dose of 30 mg/kg twice daily for 3 days, starting 2 days before the anticipated noise event and continuing through the event. Pharmacokinetic data have previously been submitted for this product to support an indication 'for the reduction of the frequency of generalised seizures…'. As the maximum daily dose for this approved indication is the same as that proposed for the noise phobia indication, these pharmacokinetic data also support the new indication. These data support the proposed twice-daily dosing regimen and the values for the key pharmacokinetic parameters. No additional pharmacokinetic studies are required.

2.3.3. Target species tolerance

Previously submitted data support the safety of imepitoin in the dog at 1, 3, and 5 times the maximum recommended dosage of 30 mg/kg twice daily, for the anti-epilepsy indication (Bassett, 2008). The applicant references this study in support of the proposed indication for 'noise phobia'. It supports target species tolerance at doses of up to 5 times the maximum recommended dose of 30 mg imepitoin/kg bodyweight for an extended period of six months. An additional GLP target species safety study is therefore not necessary.

2.3.4. Dose determination

The applicant has provided four dose characterisation studies in the dog to justify the proposed dosing regimen. These studies are considered individually below.

Study 1: An exploratory field study was conducted in Germany in dogs with generalised anxiety disorders to evaluate the anxiolytic effects of imepitoin after administration at a dose of 20 mg/kg twice daily for 3 days. The GCP status of the study was not declared. Sixty dogs were randomised to receive either imepitoin or placebo. The study was blinded. Anxiolytic efficacy was evaluated based on serum cortisol levels, change in behaviour score, and the owner's assessment of the behaviour change. Adverse events were recorded. Statistically significant reductions ($p<0.05$) in cortisol levels were seen after 3 days treatment with imepitoin. There was an absence of any significant behavioural improvement. Despite this, the results are overall considered to indicate potential for an anxiolytic effect in the dog, taking into consideration the potentially greater therapeutic challenge to control anxiety and fear in dogs with a generalised condition and the lower dose administered during the study (20 mg/kg twice daily). No serious adverse events (AEs) occurred during this study and the incidence of other AEs was similar in the placebo and imepitoin treatment groups. In summary, the results of this study are suggestive of the potential for an anxiolytic effect of imepitoin after 3 days treatment; however, the results suggest that the dose of 20 mg/kg may be inadequate.

Study 2: A baseline-controlled case series conducted in dogs to evaluate the anxiolytic efficacy of imepitoin alongside a behaviour modification programme for the treatment of fear/anxiety related behaviour problems. All dogs were treated with imepitoin at a starting dose of 10 mg/kg twice daily and the dose was increased until either sufficient efficacy was achieved or a maximum dose of 30 mg/kg twice daily was reached. Dogs were treated for 11 weeks and doses were adjusted according to response every 2 weeks. The primary efficacy endpoint was average weekly global fear-anxiety reaction scores. A statistically significant response to treatment ($p<0.001$) was observed for the 17 evaluable dogs based on a comparison of the results for the primary efficacy endpoint at week 1, week 11 and the decision point with the results at baseline. While this response was seen as early as week 1, the size of the decrease in global fear-anxiety reaction score relative to baseline was larger at

the end of the study. This corresponds with the point in the study when higher mean doses of imepitoin were being administered and the behavioural programme would have had time to manifest results. At the end of the study most dogs received either a dose of 20 or 30 mg/kg twice daily (59% and 23% of dogs respectively). Contrary to the longer-term use of imepitoin during this study, the applicant proposes short-term treatment courses for noise phobia. There would therefore be no opportunity to titrate the dose to effect when using the product for a predictable noise event in the future, requiring the selection of the dose with the greatest probability of achieving anxiolytic efficacy. This study therefore supports the use of a higher dose of 30 mg/kg twice daily for noise phobia. Six adverse events were reported in treated dogs during this study; ataxia and diarrhoea were considered most likely to be attributable to treatment. The safety of the product in treated dogs was acceptable based on the results of this study.

Two laboratory studies, conducted in healthy Beagles, evaluated the anxiolytic efficacy of imepitoin based on an open field activity test (thunderstorm test). Cortisol and activity scores (distance travelled, inactivity duration, and inactivity frequency) were used to reflect the level of anxiolytic efficacy. Adverse events were also recorded.

Study 3: The study first evaluated the efficacy of a single imepitoin dose of 20 mg/kg *per os* given to fasted dogs with tests conducted at the time of expected maximal plasma imepitoin concentrations (2 hours post-treatment). The study did not include a control group. Anxiolytic efficacy was evaluated based on a comparison to baseline in individual dogs. A significant decrease in absolute cortisol levels at the end of the thunderstorm test was seen in 13/16 dogs. Changes in activity scores (distance travelled, inactivity duration and frequency) were evaluated based on anxiety phenotype (hyperactive or hypoactive) and were found to be significant for the hypoactive group but not the hyperactive group. This may reflect a difference in the responsiveness of these populations; further work would be necessary to test this hypothesis. Overall, the results of this study are suggestive of the presence of anxiolytic effects of imepitoin after a single dose of 20 mg/kg bodyweight. However, the results of this study must be interpreted cautiously given its uncontrolled nature, the small numbers of dogs treated, and the fact that the treated animals were healthy Beagle dogs (no diagnosis of noise phobia).

Study 4: a second, placebo controlled study evaluated the efficacy of imepitoin at a dose of 20 and 30 mg/kg twice daily *per os* for 4 days in healthy Beagles. However, during this study the thunderstorm tests were conducted at 4 hours when the applicant considered plasma imepitoin to be at levels below the maximal concentration and more consistent with the reality of use. Testing was performed on days 1 to 4 of the study. The analysis of the cortisol results did not provide any conclusive results, in part due to the presence of a significant response in the placebo group. No significant differences between treatment groups were observed for the comparison of cortisol post-test levels and change in cortisol (post-test minus pre-test level). Changes in activity scores (distance travelled, inactivity duration and frequency) relative to baseline were not significant for the placebo treated animals. Results for these measures in the two treatment groups were consistent with an anxiolytic effect. For example, a significant difference relative to baseline and between groups was observed for distance travelled, supporting an anxiolytic effect in the two imepitoin treatment groups. Overall, the results of this study support a superior anxiolytic efficacy of imepitoin at a dose of 30 mg/kg twice daily compared with a dose of 20 mg/kg twice daily. The applicant has reported that the pharmacological effect of imepitoin appeared more pronounced after 3-4 days; however, this trend is not robustly demonstrated.

The data presented suggest that a dose of 30 mg/kg twice daily would provide anxiolytic efficacy and suggest that efficacy at 20 mg/kg is lower and potentially inadequate. The applicant’s conclusion that 'the shortest required time to achieve optimal efficacy was shown to be two days before the day of the anticipated event' is not fully supported by the study results. However, while the onset of anxiolytic

efficacy may occur before 2 days of treatment are completed (study 4), the applicant's proposed pre-treatment period is supported since it is accepted that efficacy may be suboptimal in some dogs before 48 hours; a warning is proposed for section 4.4 of the SPC to this effect. Furthermore, many of the adverse events associated with treatment occur soon after initiation of therapy and, in most cases, these will have resolved prior to the occurrence of the anxiety-eliciting noise event. This is considered to be beneficial for the treatment response.

2.3.5. Dose confirmation / Field trials

To confirm the safety and efficacy of imepitoin at a dose of 30 mg/kg twice daily for 3 days for the control of anxiety and fear associated with firework noises in dogs, the applicant has provided one pivotal GCP field trial. This study was a placebo controlled field study conducted in client-owned animals at 21 sites across Germany and the Netherlands over the New Year period (December 2016). Animals were selected based on owner reported fear and anxiety to explosive noises shown consistently in the home and in the owner's presence and a Lincoln Sound-Sensitivity Scale (LSSS) score above 30. Dogs meeting all eligibility criteria were randomly allocated to treatment groups (imepitoin or placebo). Dogs were dosed according to bodyweight across a dose range from 17.2 to 40.0 mg/kg twice daily for 3 days based on a proposed dosing chart for the noise phobia indication. The median dose rate actually administered during this study was 30 mg/kg in the imepitoin treatment group (range 20.0 - 40.0 mg/kg). However, only 8/104 imepitoin treated dogs received a treatment dose below 25 mg/kg. In view of the limited support provided for the efficacy of the lowest doses administered during the pivotal field trial, the dosing table proposed for the SPC and package leaflet will restrict the dosing range to between 25.0 and 40.0 mg/kg. The co-primary efficacy endpoints were owner assessed overall effect (ordinal variable scored from 1-5) and evolution of anxiety score across the study period (expressed as the mean difference in anxiety score between treatment groups). The anxiety scoring system used was based on the Lincoln Sound-Sensitivity Scale, a well-recognised approach to assessing anxiety. This anxiety score was the sum score of 16 behaviours, each behaviour scored by the owner on a scale from one to five during a 15 minute assessment period (baseline, 31 December at 16:00 and 22:00 hr, and 01 January at 0:20 and 1:00 hr). Both the co-primary endpoints have been shown to be valid measures of the anxiolytic efficacy of medicinal products in dogs. 251 dogs were enrolled; 13 dogs were excluded as they were not treated once and the remaining 238 dogs formed the EU Safety Population (EU-SAF). After 12 exclusions due to lack of any data to allow evaluation, 226 dogs formed the EU Full Analysis Set (EU-FAS). A statistically significant difference ($p<0.05$) between the imepitoin (Investigational Veterinary Product; IVP) and placebo (Control Product; CP) treatment groups was shown for both the first and second co-primary endpoints at the EU-FAS population level. A significantly larger proportion of owners in the imepitoin group reported a good or excellent effect (64.4%), compared with owners in the placebo group (25.4%). The cumulative odds for a good or excellent effect (owner assessed overall effect) were significantly greater for the imepitoin treatment group than for the placebo treatment group. The cumulative odds ratio was 4.689 (95% CI: 2.79-7.89), in favour of superiority of the IVP over placebo ($p<0.0001$). Worsening of the condition was reported in 3.8% of the treated dogs (versus 4.9% in the placebo group) and absence of effect in 15.4% of treated dogs (versus 49.2% in the placebo group).

The mean difference in anxiety score across all time points after baseline was -6.1 (95% confidence limits -8.6 and -3.6) supporting superiority of imepitoin over placebo (adjusted mean anxiety scores were 11.7 (±0.94) for the imepitoin group and 17.8 (±0.87) for the placebo group). An analysis at the EU-PPS (Per Protocol Set) level also confirmed the results at the EU-FAS level. These results for both the co-primary endpoints exceed the predefined thresholds for clinical significance set *a priori* and confirm that superiority to placebo is also clinically meaningful. The outcomes for the secondary efficacy endpoints were also supportive of the results for the co-primary endpoints. AEs were reported

appropriately by the applicant. The incidence of AEs in the imepitoin treated animals was significantly higher with 48.2% of dogs in the IVP group experiencing at least one AE compared with 10.5% of CP group dogs. None of these AEs were classified as serious by the applicant; no deaths or euthanasia occurred due to treatment. The most common AE was ataxia (35.1% IVP versus 1.6% CP). In all cases, this was observed on the first day within a few hours of starting treatment. In 75.6% of cases, the AE resolved within 48 hours under continuous treatment. In 11 dogs, the occurrence of ataxia resulted in treatment with imepitoin being withdrawn (n=6) or the treatment dose being reduced by the investigator (n=5). These ataxia AEs have been included in the SPC (section 4.6). The other commonly observed AEs in the IVP group included increased appetite, lethargy, emesis, and hyperactivity; these AEs are also included in the SPC. Three AEs in three dogs were coded as aggression (incidence 2.6% in the IVP group compared with 0% in the CP group). Aggression is listed as a potential AE in the SPC (section 4.6). In addition, the applicant has proposed additional risk mitigation measures for the SPC. Overall, the results are supportive of an acceptable safety profile of Pexion for the noise phobia indication in dogs. However, the initially proposed indication, ''For the control of anxiety and fear associated with noise phobia in dogs' was modified during the regulatory review to read, 'For the reduction of anxiety and fear associated with noise phobia in dogs'.

2.3.6. Overall conclusion on efficacy

The pivotal field trial tested the efficacy of Pexion (imepitoin) at a median dose of 30 mg/kg twice daily for 3 days starting 2 days before the anticipated noise event (New Year's Eve fireworks) in a population of dogs with established noise phobia to fireworks. Based on both the owner assessed overall effect of treatment and the reduction in anxiety scores (treatment versus placebo), a statistically significant and clinically relevant anxiolytic effect was observed, supporting an indication for 'reduction of anxiety and fear associated with noise phobia'.

3. Benefit-risk assessment of the proposed change

This product is authorised for the reduction of the frequency of generalised seizures due to idiopathic epilepsy in dogs for use after careful evaluation of alternative treatment options. The active substance is imepitoin, which inhibits seizures via potentiation of the $GABA_A$ receptor-mediated inhibitory effects on the neurons.

The proposed variation is to add a new therapeutic indication: 'For the reduction of anxiety and fear associated with noise phobia in dogs'. The grouped variation is also to add a new pack-size of 30 tablets for Pexion 100 mg tablets and for Pexion 400 mg tablets and to additionally introduce changes in the specification parameters of the immediate packaging.

In the framework of this variation, product information is being aligned with QRD template v. 8.1 and changes are implemented following the renewal procedure and a type IB variation. Amendments are also made in alignment with the assessment of the 7th PSUR for the product.

3.1. Benefit assessment

Direct therapeutic benefit

As reported in the CVMP's assessment of the product for existing indication of epilepsy, imepitoin is a centrally acting substance with anxiolytic and antiepileptic properties. Imepitoin 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 ($GABA_A$ receptor) that mediates the anxiolytic effect of imepitoin. Imepitoin also inhibits seizures via potentiation of the $GABA_A$ receptor-mediated inhibitory effects on the neurones and, in addition, imepitoin has a weak calcium channel blocking effect that may contribute to its anticonvulsive properties.

A well-conducted placebo-controlled clinical trial conducted in accordance with GCP and with a treatment duration of 3 days demonstrated that the product is efficacious in reducing the anxiety and fear associated with explosive noises (fireworks) when administered to dogs with a history of reacting to fireworks or other loud explosive noises. This benefit was supported based on an evaluation of owner assessed overall effect of treatment (cumulative odds ratio for good or excellent effect of 4.689 in favour of superiority of the IVP over placebo ($p<0.0001$)) and the mean difference in anxiety score relative to placebo during a period of exposure to explosive noises (mean difference -6.1 (95% confidence limits -8.6 and -3.6)). These results are supportive of the superiority of the IVP over placebo and support the anxiolytic efficacy of a nominal dose of 30 mg/kg twice daily (range 25.0 - 40.0 mg/kg twice daily) 'for reduction of anxiety and fear associated with noise phobia'.

3.2. Risk assessment

Quality:

Information on the variation has been presented in a satisfactory manner.

Safety:

Risks for the target animal:

Adverse events reported during pre-clinical and clinical trials to support the noise phobia indication are supportive of the existing SPC warnings. During the pivotal field study, the most common side effects following treatment (30 mg imepitoin/kg bodyweight *per os* twice daily for 3 days) were ataxia, increased appetite, lethargy, emesis, and hyperactivity. Ataxia, the most commonly observed adverse event, was not considered serious and resolved in 75.6% of cases within 48 hours under continuous treatment. All the adverse events that occurred in dogs treated with the recommended dose are already listed on the authorised SPC. Three adverse events in three dogs treated with imepitoin (incidence 2.6%) were coded as aggression; additional risk mitigation measures are included in the SPC. Appropriate sentences are also included for the other adverse events observed.

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.

Risk for the user:

As the product will be administered to the same target species at the same dose rate and at the same frequency as already approved for the existing indication, no new risk is considered to arise in terms of user safety. Therefore, the user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

Risk for the environment:

The product is not expected to pose a risk for the environment when used according to the SPC recommendations.

3.3. Risk management or mitigation measures

Appropriate sentences are already included in the SPC for many of the adverse events observed during the pivotal field study conducted to support the 'noise phobia' indication. Further risk mitigation is proposed for the risk of aggression following treatment with imepitoin in dogs with noise phobia.

3.4. Evaluation of the benefit-risk balance

The benefits of Pexion for the reduction of anxiety and fear associated with noise phobia in dogs have been supported by the results of a pivotal field trial in the target population. The benefits of imepitoin for noise phobia are considered to be adequately supported.

Overall, the safety profile of Pexion administered *per os* at a dose of 30 mg imepitoin per kg bodyweight twice daily for 3 consecutive days for treatment of noise phobia is considered to be satisfactory. The most common adverse event, ataxia, was not serious and resolved in 75.6% of cases within 48 hours under continuous treatment. All the adverse events likely to be attributable to treatment with imepitoin are already listed on the SPC (section 4.6).

The benefit-risk balance remains positive.

4. Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Pexion can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows:

- Addition of a new therapeutic indication: 'For the reduction of anxiety and fear associated with noise phobia in dogs';
- Addition of a new pack-size of 30 tablets for Pexion 100 mg tablets and for Pexion 400 mg tablets;
- Introduction of changes in the specification parameters of the immediate packaging;
- Alignment of product information with QRD template v. 8.1 and following the renewal procedure (EMEA/V/C/002543/R/0010), a type IB variation (EMEA/V/C/002543/IB/0012) and the assessment of the 7th PSUR.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I, IIIA, IIIB and A.