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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Pexion (EMEA/V/C/002543/0000)

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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Introduction

An application for the granting of a community marketing authorisation of Pexion was submitted to the Agency on 28 September 2011 by Boehringer Ingelheim Vetmedica GmbH. This application was submitted under Article 3(2)(a) of Regulation (EC) No 726/2004 in accordance with Article 12(3) of Directive 2001/82/EC as amended as it contains a new active substance which has not previously been authorised in the Community. The eligibility to the centralised procedure was agreed by CVMP on 5-7 April 2011.

The CVMP adopted an opinion and CVMP assessment report on 13 December 2012.

On 25 February 2013, the European Commission adopted a Commission Decision for this application.

Pexion contains imepitoin as the active ingredient and is presented as tablets in strengths of 100 mg/tablet and 400 mg/tablet. Both tablet strengths will be available as packs/containers of 1 bottle containing either 100 tablets or 250 tablets. The route of administration is oral use. The target species is dogs.

The product is indicated for the reduction of the frequency of generalised seizures due to idiopathic epilepsy in dogs for use after careful evaluation of alternative treatment options.

New active substance status

The active substance imepitoin in Pexion is considered a new active substance.

Licensing status

Pexion was not licensed in any country in the EU at the time of submission of the application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The description of Boehringer Ingelheim Animal Health's pharmacovigilance system submitted fulfils the current legal requirements, as described in the addendum of Volume 9 B of The Rules Governing Medicinal Products in the European Union related to the guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections for veterinary medicinal products published by the Commission in March 2007.

Manufacturing authorisations and inspection status

Declarations of compliance of the manufacture of the product with EU GMP requirements have been provided. An inspection prior to authorisation is not necessary.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites are considered in line with legal requirements.

Part 2 – Quality

Composition

Pexion 100 mg and 400 mg tablets for dogs contain imepitoin as active substance. The tablets are white, oblong shaped and half scored with embedded logo "I 01" (100 mg) or "I 02" (400 mg) on one side. The tablet can be divided into equal halves. Conventional tablet pharmaceutical excipients are used: microcrystalline cellulose, hypromellose, lactose monohydrate, sodium starch glycolate, magnesium stearate and purified water. All the excipients have been previously used in the manufacture of authorised oral veterinary medicines.

Container

For the 100 mg tablets:
35 ml and 60 ml high density polyethylene (HDPE) bottles are filled with 100 or 250 tablets, respectively, and a desiccant canister. The bottles are capped with polypropylene (PP) child tamper-proof screw closures.

For the 400 mg tablets:
100 ml and 250 ml HDPE bottles are filled with 100 or 250 tablets respectively, and a desiccant canister. The bottles are capped with PP child tamper-proof screw closures.

The packaging materials in contact with the tablets are certified to comply with both, Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs, and current European Pharmacopoeia (Ph. Eur.) requirements.

Development pharmaceutics

The active substance imepitoin is manufactured in Europe and has never been used in human medicines in the EU.

Imepitoin is a white to almost white, solid, non-hygroscopic substance without odour or bitter taste. It is practically insoluble in water. The necessity of higher dosages required for therapeutic effects lead to the manufacture of uncoated tablets of 100 mg and 400 mg strengths using the same dose-proportional composition of the final blend for compression (homologous principle).

The choice of suitable excipients focused on the requirements resulting from the active substance characteristics and intended formulation. Based on stability results of imepitoin in the presence of various fillers, binders, disintegrants, anti-adherents and lubricants suitable excipients have been selected. Purified water is evaporated during the drying process and consequently not included in the final dosage form. No further excipients were required to improve the acceptability by dogs of the Pexion tablets, taking into consideration that the drug substance has neither bitter taste nor unpleasant odour.

The blended granulate was found suitable for compression in order to obtain oblong half-scored tablets containing 100 mg and 400 mg of imepitoin, respectively, providing the possibility to accurately administer the required dose. Differentiation between both strengths is ensured by the different tablet sizes and the embossed codes ("I 01" for the 100 mg tablets, "I 02" for the 400 mg tablets). The suitability of the score line has been demonstrated by the results of the test for subdivision of tablets performed on three batches of each of both strengths according to the Ph. Eur. requirements.

Method of manufacture

Detailed descriptions of the manufacturing process have been provided.

The applicant agreed to perform the validation of the compounding and tabletting process of the first three consecutive production batches.

Control of starting materials

Active substance

The active substance imepitoin (INN) is a new chemical entity. Its chemical name is 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one. The active substance has no chiral centers, and stereoisomers do not exist. Imepitoin is non-hygroscopic, practically insoluble in water, sparingly soluble in 0.1N HCl and methanol, and slightly soluble in dimethylformamide.

Evidence of structure has been confirmed by several methods.

Imepitoin is produced, using commercially available high purity starting materials. Comprehensive information was provided on the quality of the materials, reagents and solvents as well as on potential impurities of the active substance imepitoin formed in the synthesis steps and including the starting materials and residual solvents. The relevant residual solvents are controlled according to the relevant VICH criteria. All impurities are also appropriately controlled. The data provided are satisfactory.

The validations of the analytical methods used for control of the active substance are considered satisfactory and in compliance with relevant VICH guidelines. The studies performed confirm the validity of the analytical methods.

Stability of the active substance has been supported by results from three production scale batches. All these studies have been completed. The appearance, the loss on drying, the colour, clarity and opalescence of solution, and the potency (assay) are unchanged over the course of 60 months. Microbial test results after 60 months storage are in accordance with the specification. A re-test period of 60 months at temperatures not exceeding 25 °C/60%RH is accepted based on the submitted data.

Excipients

All excipients (lactose monohydrate, cellulose microcrystalline, hypromellose, magnesium stearate and sodium starch glycolate) are compliant with their respective Ph. Eur. monographs and requirements.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

A declaration was provided stating that Pexion tablets comply with the latest version of the CPMP/CVMP Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 3). All excipients are either of vegetable or chemical origin with the exception of lactose. However, in light of current scientific knowledge and irrespective of the geographical origin, bovine milk is unlikely to present any risk of contamination.

Control tests during production

The in-process controls are satisfactory.

Control tests on the finished product

The specification includes all of the tests expected for a tablet and is in line with the respective guideline. The specifications proposed at release are suitable to control the quality of the finished product. The shelf-life and release specifications are not the same. The limits for assay and related substances are widened at end of shelf-life. The same analytical methods are used for shelf-life and release specifications. The specification limits for water content, related compounds and the assay limits for the end of the shelf-life were accepted by the CVMP with the agreement that they are re-assessed as a post-marketing recommendation once more data have been generated for the product at the final manufacturing site.

The uniformity of dose for tablet halves was proven according to Ph. Eur. requirements with pilot batches.

All analytical methods are fully described and validated according to VICH requirements.

Batch analysis data are presented for 3 batches of each tablet strength, manufactured at the finished product manufacturer. All batches demonstrate full compliance with the proposed specifications.

Stability

Stability tests are performed according to VICH requirements; the analytical methods are validated.

Stability data of accelerated (6 months at 40 °C/75% RH) and long term (up to 18 months at 30 °C/65% RH and 25 °C/60% RH) stability testing are available for 3 batches each of Pexion 100 mg and 400 mg tablets for dogs.

Additionally, stability data from accelerated (40 °C/75% RH) and long-term testing (30 °C/70% RH and 25 °C/60% RH) up to 36 months are presented for 3 pilot batches each of Pexion 100 mg and 400 mg tablets for dogs.

The dissolution profiles remain compliant with Ph. Eur. requirements.

A shelf-life of 30 months is justified according to the guideline EMEA/CVMP/QWP/846/99-Rev.1. The applicant agreed to re-assess the specifications once more stability data are available following completion of the manufacture of the first industrial batches at the manufacturer of the finished product.

In-use stability tests were performed on one batch of each strength under long-term storage conditions (25 °C, 60% RH). Stability results covering 250 days in-use testing conditions demonstrate that the tablets can be kept in periodically opened bottles for the recommended storage conditions for 250 days (8 months). The stress stability test does not induce changes.

No stability data for halved tablets were provided. Pexion tablets are foreseen to treat a life-long condition and the tablets are administered twice daily. The expected time that a tablet half remains in the container would be the time between two doses (approximately 12 hours). This is considered acceptable, given that the in-use stability is 250 days for the undivided tablets. Additionally the sentence *"Use any divided tablet at the next administration time"* is included in section 6.3 of the SPC.

Photostability tests were performed for 2 batches each of Pexion 100 mg and 400 mg tablets for dogs in accordance with the current specification. The tablets primary packed in the HDPE bottles as intended for marketing were subjected for 24 hours to light according to the relevant VICH guideline. No changes were observed in any of the parameters tested. The container closure system ensures the

protection of the finished product against light irradiation since this packaging system is completely impenetrable to light.

No special storage conditions are required.

Overall conclusions on quality

Pexion 100 mg and 400 mg tablets are half-scored in order to provide a wide and accurate dosage range at the recommended dosage of 10-30 mg/kg bw orally, administered twice a day.

The manufacturing process is a granulation followed by compression. Detailed descriptions of the pharmaceutical development are provided. All raw materials and excipients are compliant with Ph. Eur. monographs.

The specifications at release are satisfactory. All analytical methods are validated according to VICH requirements and stability tests are performed according to VICH requirements.

A shelf-life period in bottles before first opening of 30 months is justified. The proposed in-use stability of 250 days (8 months) for the tablets is acceptable.

The applicant agreed to re-assess the specifications once more data will have been generated for the product at the final manufacturer as post-marketing recommendation.

Part 3 – Safety

Safety documentation

Pharmacodynamics

Primary pharmacodynamic effects

The mode of action of imepitoin as anticonvulsant is described through a series of studies performed with different in vitro, ex vivo and in vivo models and by comparison with different reference substances (e.g. benzodiazepine antagonists, agonists, convulsants).

Mechanism of action:

Studies showed that imepitoin is a centrally acting antiepileptic substance which acts as a low affinity partial agonist on the benzodiazepine binding site of the $GABA_A$-receptor. In vitro studies showed a weak affinity for the benzodiazepine receptor, approximately 600 times less than diazepam.

Imepitoin potentiates the amplitude of $GABA_A$- receptor-mediated inhibitory effects on the neurons, and thereby prevents seizures. Moreover, a weak inhibition of neuronal calcium channels may contribute to its pharmacological activity (anticonvulsive properties).

Anticonvulsant activity:

Imepitoin has anticonvulsant activity against electrically and chemically induced seizures after intraperitoneal and oral administration and in genetic models of epilepsy. Imepitoin exerts also pronounced anticonvulsant activity in models for partial seizures and in models of absence epilepsy. The effective dose varies between 1 and 100 mg/kg depending on the model used.

Secondary pharmacodynamic effects

The following secondary pharmacodynamic properties have been observed for imepitoin:

- An anxiolytic effect in different models in rats at doses around 3-30 mg/kg.
- No sedative activity at these doses but only at 300 mg/kg.
- A low potential to induce CNS suppression.
- No effect on gastrointestinal transit time.
- Diuretic activity in rats was observed only at high dosage (100 mg/kg).
- Reversible interaction with the hERG-mediated potassium channel (implicated in the prolongation of QT interval).
- Increase of heart rate and at higher doses (100 and 300 mg/kg) unspecific cardiodepressive effects in dogs.
- No impact on ECG parameters or irregular beats after one single dose of 30 - 300 mg/kg in dogs.

Pharmacokinetic properties

Several single/multiple administration and metabolism studies with dogs and rats were provided, not all of them GLP compliant. These studies were not performed with the final product but with imepitoin in gelatine capsules or as suspension. The doses were 10 mg/kg to 215 mg/kg in dogs and 20 mg/kg to 30 mg/kg in rats

They showed:

- No pharmacokinetic gender differences.
- High pharmacokinetic variability between animals.
- In dogs, imepitoin is excreted via the faecal route rather than via the urinary route after oral and intravenous administration.
- The oral bioavailability of labelled imepitoin in capsules is estimated at about 92% based on the renally excreted fractions from 3 animals.
- In rats, T_{max} and $t_{1/2}$ are similar in the plasma and in the brain.
- In dogs, after oral administration at 20 mg/kg/day during 10 days, the accumulation ratio of AUC and C_{max} is below 1.
- In dogs, the pharmacokinetics of imepitoin is linear between 10 and 316 mg/kg after one daily oral administration.

One pivotal pharmacokinetic GLP study was performed with the final product in the target species after single or multiple oral administrations. This study investigated the comparative pharmacokinetics of imepitoin, following repeated oral dosing, when it was administered twice daily at 30 mg/kg to fed or fasted dogs. The study was conducted in 12 dogs, males and females, in a cross-over design.

The main findings were:

- Co-administration of imepitoin tablets with food reduces the total AUC by 30% and the C_{max} by 15% but produces no change in T_{max}.
- Only C_{max} is significantly different between males and females with a higher C_{max} for females. In the other PK variables gender specific differences do not occur.
- The steady-state after twice-daily dosing seems to be achieved following two days of treatment (at 30 mg/kg during five days), meaning no difference in C_{max} between the second administration and the following ones.
- No accumulation occurs after 4 days: AUC_{inf}: 101 407 hr.ng/ml (D0) versus 61 661 hr.ng/ml (D5). This was expected since the elimination half-life is about 2 hours.

The applicant justified the dose with clinical studies (see clinical part).

Toxicological studies

Single dose toxicity

The acute toxicity of imepitoin was assessed in rats and mice after intraperitoneal or oral administration. After oral administration, no mortality was noted in both species up to 2105 mg/kg. After intraperitoneal administration, mortality was reported at 1000 mg/kg for mice and at 464 mg/kg in rats.

Signs of intoxication after oral or intraperitoneal administrations were similar and were mainly related to pharmacological activity of imepitoin: disturbances of the central nervous system (hypokinesia, decreased muscle tone, loss of reflexes), decrease of body temperature, weight loss, excessive salivation and discoloration of faeces.

These signs were reversible within some days (maximally up to 11 days) after administration.

Repeated dose toxicity

Several GLP compliant studies on repeated dose toxicity were provided on target and non-target species (dogs, rats and monkeys).

In a GLP compliant 4 week toxicity study in 32 dogs, imepitoin was administered orally in doses of 0, 31.6, 100 or 316 mg/kg imepitoin/day as gelatine capsule.

At the two highest dosages vomiting, electrocardiogram (ECG) modifications (prolongation of the QT interval) and coordination disturbances were reported. At the highest dosage, other effects were: central nervous system disturbances (decrease of motor activity), excessive salivation, decrease of food consumption and body weight, decrease of heart rate and body temperature, haematological changes (signs of regenerative anaemia), signs of affection of the liver (increase of cholesterol, triglycerides, total protein, albumin) and of kidney (increase of creatinine) were observed. These signs were reversible after a 6 week recovery period. Histopathological findings were observed at the two highest dosages with a dose-dependent severity and were seen in liver and lymphoid organs.

At the highest dose only, in males sexual organs atrophy of seminiferous tubules, decreased sperm content in epididymis and prostate atrophy were found; in females swollen mammary glands were found. The lesions noted in the liver and in sexual organs were not totally reversible after 6 week recovery period. No information was given on the reversion of lesions in lymphoid organs. Cardiac

effects (slightly increased mean value of QT and heart rate corrected QT-intervals) were reported from 100 mg imepitoin/kg daily dose. No clinical signs and no histopathological findings were reported at 31.6 mg/kg that can be retained as a NOEL for this study.

Even though the study was not performed with the final formulation, it is the opinion of CVMP that these effects might not have been related to the formulation but rather to the active substance, considering the pharmacological properties of imepitoin. Hence, these observations are added in the SPC (section 4.10).

In a GLP compliant 13 week study, dogs received imepitoin in gelatine capsules at doses of 0, 31.6, 82.5 and 215 mg/kg/day. The period treatment was followed by a 6 week recovery period. The study was conducted in accordance with OECD guideline Test No. 409. Vomiting was reported at all doses including control. Mydriasis was noted from 82.5 mg/kg. Other clinical signs and observations in the highest dose group (316 mg/kg) were similar to those recorded in the 4 week oral toxicity study in dogs and consisted in signs of central and autonomic nervous system's disturbances (hypokinesia, coordination disturbances, excessive salivation), decreased food consumption and body weight, signs of regenerative anaemia, effects on heart and ECG. A new finding was vacuolisation in kidneys of male dogs of all groups, including the control one. The incidence and severity increased with the dose and the lesion persisted after the 6 week recovery period in the control and the highest dose group. Mydriasis was reported from 82.5 mg imepitoin/kg daily dose. This dose corresponded to 2.75 times the maximal recommended dose which is 30 mg/kg twice daily (bid).

No NOEL can be retained from this study as vomiting occurred once only in females at the lowest tested dose. Hence, the NOEL is < 31.6 mg/kg and the LOEL is 31.6 mg/kg. This indicates a low safety margin of imepitoin for dogs. Even though the study was not performed with the final formulation, CVMP is of the opinion that these effects might not have been related to the formulation but rather to the active substance. Hence, these observations are added in the SPC (section 4.10).

As cardiac effects of imepitoin (ECG changes with prolongation of the QT interval) were observed in Beagle dogs after prolonged high dose exposure (see 4 week and 13 week oral toxicity study in dogs), the effect of imepitoin was further evaluated in three in vitro studies and one in vivo study in anesthetised dogs. The in vitro studies showed that imepitoin exerts a weak calcium channel blocking action. In the in vivo study the effect of 30 - 300 mg/kg imepitoin on haemodynamic and respiratory parameters was investigated in anaesthetised, spontaneously breathing beagle dogs for 240 minutes after intraduodenal administration. Following administration of 100 and 300 mg/kg of imepitoin, nonspecific weak cardiodepressive effects were observed. Additionally, the administration of these doses led to a significant fall in lung compliance. In all experiments with imepitoin, no changes in ECG parameters or irregular beats were noted. 30 mg/kg of imepitoin was the no effect dose in this study. This dose is the highest therapeutic dose recommended for Pexion but as it was administered only once, the extrapolation to possible cardiac effects after repeated administrations is difficult.

In a GLP compliant 4 week toxicity study, rats (5 male, 5 female) received 0, 31.6, 100 or 316 mg/kg imepitoin/day in an aqueous suspension by gavage for 28 days. The protocol of the study was in accordance with OECD guideline Test No. 407. Adverse reactions were observed at the two highest doses. The occurrence and severity were dose-dependent. At 100 and 316 mg/kg disturbances of coordination were noted. At the highest dosage, hypokinesia, disturbances of the automatic nervous system, the haematological system (at the beginning of the treatment increase in red blood cells, haematocrit and absolute values in platelets and from 4 weeks of treatment, a decrease of these parameters were observed), excessive salivation were recorded. These signs were not observed after the 6 week recovery period. Reversible signs of hepatotoxicity were observed in males. Eyes were also affected by the treatment at the highest dose with permanent diffuse retinal atrophy. Macroscopic

findings were observed at the highest dose only and were noted for male sexual organs and for heart in both sexes (dilatation). Microscopic examination revealed lesions in liver, eyes, sexual organs of both sexes, serous glands, gastrointestinal tract, thymus and bone marrow. Except for thymus and serous glands, for which the reversibility was incomplete, all other findings were totally reversible after 6 week reversibility period. No adverse effects or product related histopathological findings were observed at 31.6 mg/kg. This value was retained as a NOEL.

In a GLP compliant 13 week toxicity study, rats received 0, 31.6, 100 or 316 mg/kg imepitoin/day by oral gavage. The protocol of the study was in accordance with requirements of OCDE guideline Test No. 408. All observations made in this study are in correlation with those recorded in the 4 week oral toxicity study in rats and dogs (see the previous studies). No clinical signs or histopathological findings were recorded at 31.6 mg/kg that can be retained as a NOEL for this study.

A further GLP compliant 13 week toxicity study was conducted following the retinal findings observed in the 4 and 13 week toxicity studies in rats. Effects of the test product were assessed in pigmented rats (Brown Norway rats) and non-pigmented rats (Albino Wistar rats) at high oral doses (215 and 316 mg/kg). Pigmented Brown Norway rats showed no alterations of retina or of other ocular structures up to 316 mg/kg, whereas, at this dose in albino rats retinal lesions (signs of atrophy) were recorded. They were similar to those noted in the 13 week toxicity study. Other observations (clinical signs, histopathological findings) were similar to those observed in the 13 week toxicity study. It should be noted that Brown Norway rats appeared to be more sensitive than Albino Wistar rats with regards to oral dose of imepitoin.

In a GLP compliant 13 week toxicity study conducted in Cynomolgus monkeys at a daily oral dose of 240 mg/kg/day and then of 160 mg/kg/day, imepitoin was shown to be very toxic. Within this study the potential of the test product for eye toxicity in monkeys was investigated as well. No clinical ocular sign was reported and no treatment-related lesions were seen in the retina of the eyes (including optic nerves).

Tolerance study in the target species

The applicant provided a GLP compliant tolerance study in the target species with the final formulation (100 mg and 400 mg tablets). The protocol of the study was in accordance with requirements of VICH GL 43. The certificate of analysis and raw data were provided.

The product was administered at the highest recommended dose (RD), at 3 and 5 times the RD for a 6 month period.

Vomiting and hypersalivation were observed at all groups, including the negative control one. For salivation, a dose related incidence was not noted and for vomiting the dose related incidence was not clear. However, these signs were also shown in repeated toxicity studies in dogs at a dose half of the maximal RD (31.6 mg/kg/day vs. 30 mg/kg twice daily).

Effects on eyes (prolapsed nictitating membrane) were also reported at all doses, again with a dose related incidence.

Decreased activity was observed at 3 and 5 times the RD which is in correlation with central nervous system disturbances observed in the repeated toxicity studies in rats and dogs.

At 5 times the RD, clear effects on central nervous system and on eyes, and decrease of body weight were noted.

All these effects are reported in sections 4.6 or 4.10 of the SPC.

Tolerance in target species during clinical field studies

The safety of the product was also investigated during clinical field studies as described in part 4 of this report.

Observed adverse effects were signs of effects on the central nervous system with ataxia, disorientation with disturbances of equilibrium or co-ordination, hyperactivity and restlessness. Sensory organs were also affected, with decreased sight and sensitivity to sound. Gastrointestinal disturbances such as vomiting and diarrhoea were also reported as well as musculoskeletal disorders such as decreased motor activity.

Polyphagia was also reported at the beginning of the treatment in some cases.

Increase of plasma cholesterol was observed as well. However, these did not exceed the normal reference ranges, and were not associated with any clinically significant observations or reactions. The incidence and severity of these signs were dose-related.

All these signs are stated in section 4.6 of the SPC.

An increase in creatinine levels was observed at the highest recommended dose of 30 mg/kg twice daily, however these did not exceed the normal reference ranges and were not associated with any clinically significant observations or events. As this observation was made in almost all clinical studies and in the tolerance study in case of overdose and due to the known diuretic properties of imepitoin (see preclinical part - secondary pharmacodynamic effects), the increase of creatinine levels is considered as an adverse effect and is therefore stated in section 4.6 of the SPC.

In the clinical field trials, dogs weighing less than 5 kg and dogs with safety concerns such as renal, liver, cardiac, gastrointestinal or other disease were excluded. Hence, no conclusions on the safety and efficacy for such dogs can be drawn. Therefore a respective warning sentence is included in section 4.5 of the SPC.

A contraindication for the use in dogs with severely impaired hepatic function, severe renal or severe cardiovascular disorders is included in section 4.3 of the SPC.

In the pivotal European field trial that compared the efficacy of imepitoin to phenobarbital in 226 dogs with newly diagnosed idiopathic epilepsy, 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. The most frequently reported adverse events were somnolence/sedation, polydipsia, polyuria, increased appetite, and hyperactivity.

Pexion presented the following advantages in term of safety compared to phenobarbital: fewer adverse events were noted for polydipsia (14% vs 23%), polyuria (10% vs 19%of dogs) and marked sedation (14% vs 25%) and the following drawback: more hyperactivity (16% vs 6%).

Reproductive toxicity

No formal studies on reproductive toxicity other than teratogenicity were conducted with imepitoin in any species. However, lesions in sexual organs occurred during repeated dose toxicity studies in rats and dogs which were not totally reversible after a 6 week recovery period. Therefore a warning sentence is included in section 4.7 of the SPC, stating that the use of the product is not recommended in male breeding dogs and in female dogs during pregnancy and lactation.

Two GLP studies on embryofoetal development were carried out in rats and rabbits in accordance with OECD guideline 414. In both rats and rabbits, embryo/foetotoxic effects were observed at maternal toxic doses. For rats, a NOAEL for maternal toxicity and foetotoxicity of 31.6 mg/kg was established.

For rabbits, a NOEL of 10 mg/kg for maternal toxicity and a NOEL of 33 mg/kg for foetotoxicity were established.

This point led to an appropriate sentence in SPC section 4.7, i.e. the use of the veterinary medicinal product is not recommended in male breeding dogs or in female dogs during pregnancy and lactation.

Mutagenicity/genotoxicity - carcinogenicity

A suitable and relevant test battery of in vitro (Ames test, HPRT test in V79 cells and Chromosome Aberration test in V79 cells) and in vivo (Mouse Micronucleus test) GLP studies on mutagenicity with imepitoin were carried out according to OECD guidelines, resulting all in negative results.

Furthermore, imepitoin shows no structural alert for carcinogenicity and no tumour development was observed in repeated dose toxicity studies. Therefore carcinogenicity is not considered to be a concern and no carcinogenicity study was required.

Studies of other effects

Imepitoin showed no skin sensitising properties in a maximisation test in guinea pigs.

An in vitro study showed that there was no alteration in benzodiazepine receptor binding following single or chronic treatment of mice with imepitoin. In vivo data showed that the repeated intraperitoneal (IP) administration of imepitoin at 100 mg/kg in mice does not lead to tolerance to this active ingredient contrary to diazepam. Hence, it seems that no tolerance to imepitoin appears in rodents after repeated administration.

The safety of imepitoin in humans was assessed in healthy men. Observed adverse signs were fatigue, headache, vertigo, disequilibrium, dizziness and nausea. From these studies, an overall NOAEL of 600 mg/person (i.e. 10 mg/kg for a 60 kg individual) was determined.

User safety

A user safety assessment was provided which was conducted in accordance with the current guideline on user safety for veterinary medicinal products (EMEA/CVMP/543/2003-Rev.1).

In view of the pharmaceutical dosage form, there is a very low probability of exposure via dust from the product entering the eye or the material affecting or penetrating the skin. Repeated exposure to minute amounts of imepitoin is unlikely to result in skin sensitisation as the substance gave negative results in a guinea-pig maximisation test.

Significant human exposure might occur through deliberate or accidental oral ingestion which is considered in the user risk assessment with special focus on the accidental ingestion of a tablet by a child.

When taking into account the most relevant NOEL of 31.6 mg/kg, derived from repeated dose toxicity tests in rats and dogs and applying a factor for intra- and inter-individual variation, an unacceptable risk to children would be indicated by a margin of exposure (MOE) of 0.79. Although this MOE is lower than 100, it is considered to be acceptable according to the guideline on user safety for veterinary products (EMEA/CVMP/543/2003-Rev.1) because the NOAEL was based on a repeated dose study whereas the accidental ingestion is considered a single exposure. Additionally, data on toxicity in

human adults is available, showing only mild effects such as lower blood pressure, fatigue, vertigo and headache at single administration of up to 900 mg/day for 5 days.

Appropriate warnings are included in the SPC, the package leaflet and the outer and the immediate package to prevent a risk to the user and especially to children. Furthermore, the safety of children is ensured by the presence of an appropriate child resistant closure.

Environmental risk assessment

In line with the Guideline on Environmental Impact Assessment for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98-FINAL), given that the product is:

- for individual treatment under veterinary prescription,
- the product is indicated for non-food animals,

the environmental risk assessment can stop at Phase I. It is expected that the product will not pose a risk to the environment when used as recommended.

Overall conclusions on the safety documentation

One GLP compliant pharmacokinetic study was performed with the final product in the target species after single or multiple oral administrations to fed or fasted dogs. The main results of this study are that a steady state is reached after around two days and that no accumulation occurs after that. Moreover, a food effect on the pharmacokinetic profile was noted.

The single dose toxicity studies adequately characterise the acute toxicity of imepitoin at dose rates in excess of the claimed dose in the dog. The safety margin following acute oral exposure is high.

A number of studies were presented characterising the repeated dose toxicity profile of imepitoin in the target and non-target species. The results were very homogenous, no matter which target species. Adverse effects were often similar and mainly due to pharmacological activities of imepitoin. These studies showed that the safety margin of imepitoin in dogs is low (LOAEL = 31.6 mg/kg in one study). The adverse events observed in the tolerance study and in the clinical studies are stated in section 4.6 of the SPC.

In the clinical field trials, dogs weighing less than 5 kg and dogs with safety concerns such as renal, liver, cardiac, gastrointestinal or other diseases were excluded. Hence, no conclusions on the safety and efficacy for such dogs can be drawn. Therefore respective sentences are included in section 4.5 and 4.10 of the SPC.

The adverse events seen in the pivotal European field trial as described in part 4 of this report are adequately reflected in section 4.6 of the SPC.

No single generation reproductive toxicity study has been conducted with imepitoin, neither in the target animal nor in non-target animals. However, as lesions in sexual organs of male dogs and rats were observed in the repeated dose toxicity studies which were not fully reversible, an appropriate warning for the use in male dogs intended for breeding is included in the section 4.7 of the SPC.

The safety of the veterinary medicinal product has not been established during pregnancy and lactation in dogs However, as embryotoxic effects at maternal toxic doses were found in laboratory studies in rats and rabbits, these effects are reflected in section 4.10 of the SPC and a sentence is included in section 4.7 of the SPC, stating that the use of the product is not recommended in male breeding dogs or in female dogs during pregnancy and lactation.

Imepitoin is considered as a non-mutagenic and non-carcinogenic substance.

Imepitoin shows no skin sensitising properties in a maximisation test in guinea pigs.

A user safety assessment was provided in accordance with the current guideline on user safety for veterinary medicinal products (EMA/CVMP/543/03-Rev.1). No risk after chronic dermal exposure is to be expected as imepitoin has no skin sensitizing properties. Accidental ingestion of the product might pose a risk to children. To prevent risks to the user and especially to children, appropriate warnings are included in the SPC, the package leaflet and the labelling. Furthermore, the safety of children is ensured by the presence of an appropriate child resistant closure.

The environmental risk assessment can be stopped in Phase I as the product is for individual use in dogs only. It is considered that Pexion will not pose a risk to the environment when used as recommended.

Part 4 – Efficacy

Pharmacodynamics

See Part 3.

Pharmacokinetics

See Part 3.

Dose determination/justification

The dose justification in dogs is based on laboratory studies using a disease model in dogs, and on clinical field studies in client-owned dogs treated with increasing dosage from 10 to 30 mg/kg twice daily.

The laboratory studies were based on a seizure model. The dose of imepitoin in dogs was tested in a pentylenetetrazol (PTZ) model in which the convulsant PTZ was infused intravenously at the time of expected peak plasma concentration and the dose of PTZ needed to induce a first neuronal activation resulting in seizure activity was recorded.

Two studies investigated the tolerance and dependence development during chronic administration in 7 (4 males, 3 females) and 6 (3 male, 3 female) beagle dogs, aged 6 - 10 years, respectively. Two dose levels per day of imepitoin 2x5 mg/kg and 2x40 mg/kg for 5 weeks were tested in the PTZ model. Significant increases of PTZ seizure thresholds above control thresholds were observed. The tested product was a gelatine capsule containing the active substance which is not the final formulation.

No tolerance development was observed since the threshold returned to the control level measured prior to the treatment. In the first experiment at the low dose level (5 mg/kg twice daily) the mean seizure thresholds were 54%, 33%, 59% and 45% above control on the 7^{th}, 14^{th}, 21^{st} and 28^{th} day of repeated administration, respectively. In the second experiment at the high dose level of 40 mg/kg twice daily, the mean seizure thresholds were 145%, 136%, 158% and 116% above control on the 7^{th}, 14^{th}, 21^{st} and 28^{th} day of repeated administration, respectively. This seizure model shows that the anti-convulsant effect is increased at the dose rate of 40 mg/kg bw bid compared to 5 mg/kg bid.

These studies showed that there is a dose-related anti-convulsant effect to imepitoin in dogs receiving doses of 5 and 40 mg/kg bid. Precipitated withdrawal of imepitoin therapy induced by i.v.

administration of the benzodiazepine antagonist flumazenil led to behavioural and muscular signs in some animals for one or two hours such as hyperventilation, hot-foot walking, rigid walking, rigid postures, immobility, agitation/hyperexcitation, gross body tremor, twitches and jerks. Those signs caused by a dose-dependent withdrawal syndrome precipitated with flumazenil are mentioned in section 4.5 of the SPC: "Mild behavioral or muscular signs may be observed in dogs upon abrupt termination of treatment with imepitoin."

A further laboratory study investigated the anti-convulsant activity of imepitoin in a PTZ-threshold test (seizure model) at three dose levels of 10, 20 and 40 mg/kg bw in 6 beagle dogs (3 male, 3 female, 5–9 years old). Imepitoin, as a coarse crystalline material, was administered intragastrically in a suspension of 0.5% methylcellulose in a volume of 1 ml/kg. The positive control product was valproate (150 mg/kg bw i.v.) and the negative control product was the vehicle (0.5% methylcellulose). Six dogs received each treatment successively. Significant threshold increases of 40% and 120% were obtained 1 hour after drug administration of single doses via intragastric administration of imepitoin at 20 mg/kg bw in non-micronized form, and 40 mg/kg bw in micronized form, respectively. The absence of significant threshold increase at 10 mg/kg bw may be linked to the non-micronized and non-ground form of the substance.

This single dose experiment with gavage administration indicated that micronisation improved the absorption speed resulting in earlier and higher C_{max}.

The first pilot field study includes two parts (one prospective and one retrospective part). In the prospective trial lasting 7 to 9 months, the efficacy of imepitoin was tested as a monotherapy or as an add-on therapy at various dosages with a starting dose of 5 mg/kg bw bid for 1 week and then increased dosage to 10 mg/kg. If seizures still occurred with theses doses, further increments in dosage were considered up to 30 mg/kg bw bid.

Twelve dogs with newly diagnosed epilepsy (8 males, 3 females, 1 spayed female), with a mean age of 4.6 years (from 2.5 to 13 years) of 7 pure breeds (n = 9) and of mixed breed dogs (n = 3) were included and treated with imepitoin only (monotherapy). All dogs had two or more generalized seizures before inclusion. The average dosage administered to control seizures was 20 mg/kg twice daily. Three dogs out of 12 were non responders (25%) and received dosage of 25 or 30 mg/kg bw bid. The median seizures frequency was reduced from 1.6 seizures per month (observed for less than 9 months prior onset of treatment) to 0.71 per month. A reduction of seizure frequency by more than 50% was achieved in 4 of 12 dogs (33%).

Seventeen dogs which did not respond to primary treatment with phenobarbital or primidone (conventional antiepileptics) were treated with imepitoin as an add-on therapy. The dogs were of a mean age of 4.7 ± 1.9 years old (from 1.25 to 9.5 years) of 12 pure breeds (n = 13) and mixed breed dogs (n = 4). Grand mal seizures were observed in all cases, 15 of them developed clusters of seizures, 8 dogs had acute status epilepticus, 5 had focal seizures and 2 had complex partial seizures. Ten dogs out of 17 were responders with a decrease of median seizure frequency per month from 2.4 to 1.1. A reduction of seizure frequency by more than 50% was achieved in 6 out of 17 dogs (35%).

In a retrospective follow-up data from 82 well-documented cases with newly diagnosed idiopathic epilepsy (n = 70) as well as dogs with pharmaco-resistant epilepsy (n = 12) and having be treated with phenobarbital of primidone were analysed. Among the 70 newly diagnosed cases, 26 dogs treated with primidone and 44 dogs treated with Phenobarbital were used as control dogs for the comparison with the dogs treated with imepitoin in the prospective study. A reduction of seizure frequency by more than 50% was achieved in 30/44 dogs (68%) in the Phenobarbital treated dogs and 16/26 (62%) in the primidone treated dogs. There was no control group in this study and it was

not compliant to the GCP guideline. The formulation used for the imepitoin treatment is not clearly defined although the clinical expert states that the final formulation was used. This study is considered as informative, showing the anticonvulsant efficacy of imepitoin under field conditions. No further conclusions can be drawn from this study since the design of the protocol was not adequate to show the non-inferiority of the new tested product with the conventional treatment.

As an amendment of the first pilot field, a further study details the type of seizures on which imepitoin is more effective (generalised tonic-clonic seizures). A follow-up study showed in five client owned dogs of both genders and of different breeds suffering from idiopathic epilepsy and having completed the first study that imepitoin reduces the frequency of seizure on a long term basis at individual dose rates and treatment duration varying between 10 to 30 mg/kg bw bid for 16 to 51 months.

A supportive large scale GCP compliant, randomised, double-blind, multicentre field study was designed to compare two treatment dosages of imepitoin at high-dose level (2x30 mg/kg bw) and low-dose level (2x1 mg/kg). 127 dogs with newly diagnosed epilepsy were randomised into 2 treatment groups. Approximately 65 breeds of dogs aged between 0-13 years, weighing 2-74 kg were included. No negative control group was included which would have allowed to measure the effect of the product compared to placebo. No difference between groups could be shown with a mean monthly seizures number of 2.2 and 1.8 seizures per month in the high and low dose group, respectively. As the mean baseline seizure was statistically different in the high-dose group (2.9) compared to the low-dose group (2.0), the comparison of dose effect was less meaningful. Therefore, the endpoint was modified to the change in seizure frequency relative to baseline and when considering this change to baseline seizure number, a statistically significant reduction of seizure frequency (0.9 seizures per month) was shown for the high-dose level (2 x 30 mg/kg).

In an open multicentre follow-up field study of the preceding study 53 dogs from the previous high-dose group and 47 from the low-dose group which had completed the previous study were included. A stable reduction in seizure frequency at the high-dose rate (2 x 30 mg/kg) was shown which was implemented in all dogs recruited from the preceding study and treated for over 84 days. The products used for the treatment were gelatine capsules (different from final formulation) and tablets. The frequency of adverse events was higher in the 30 mg/kg group than in the 1 mg/kg group. This study is considered as informative.

These two pilot field studies with the two follow-up studies were considered only as supportive for the dose selection since the final formulation was not used for this studies and which also did not meet the GCP compliance. The posology was defined as an initial starting dose of 10 mg/kg twice a day increased up to 30 mg/kg twice a day depending upon the treatment response of the individual dogs in the reduction of the generalized seizure frequency. The interval of dose increase of a minimum of one week of treatment was set according to clinical considerations in the treatment of epilepsy.

Field trials

US field study (supportive)

A supportive clinical field study was conducted in USA to evaluate the safety and the efficacy of the product in dogs with idiopathic epilepsy. In this trial the final formulation of imepitoin (Pexion) was compared to a product containing primidone. Imepitoin and primidone were shown to be effective in reducing seizures by ≥50% compared with baseline in more than 60% of the animals (62.4% and 84.2% for imepitoin and primidone, respectively). These results failed to demonstrate non-inferiority of imepitoin to primidone. Imepitoin was shown to be safe when used at dosages between 10 and

30 mg/kg bw bid and showed a better safety profile compared to primidone. The following adverse events occurred more often in the primidone group: hepatopathy (enzyme elevation) (16% vs 5%), ataxia (13% vs 6%), polydipsia (15% vs 3%), hyperactivity (10 vs 3%), anxiety (9% vs 3%), tachypnoea (6% vs 1%) and disorientation (5% vs 1%).

Since the positive control used in this study is not approved in the EU, the clinical data of this study was considered only as supportive evidence for the efficacy of this product.

EU field study (pivotal)

The pivotal EU field trial was a GCP compliant multicentre, comparative, randomised, blinded field study in a parallel group design, located in 29 centres in three countries (14 in Germany, 14 in France, 1 in Switzerland). The objective of the study was to confirm the efficacy and safety of the final formulation of Pexion in dogs with newly diagnosed idiopathic epilepsy, in a non-inferiority comparison with a positive control containing phenobarbital, an active substance which is authorised in several European Union countries. The treatment period was divided into two phases: a titration phase of eight weeks and an evaluation phase of 12 weeks. Before these two phases, a retrospective baseline of six weeks was recorded for each study animal. This retrospective baseline was used to determine the baseline seizure frequency before the start of the treatment. The titration phase started immediately after the inclusion of the dog into the study. During both phases, the dosage of the study treatments could be increased until the "maximum allowed dosage" was reached.

The treatment with imepitoin involved an initial dosage of 10 mg/kg twice daily. If seizures were uncontrolled, this dosage could be increased, first to 20 mg/kg twice daily and then to 30 mg/kg twice daily. The 30 mg/kg twice daily dosage represented the "maximum allowed dosage" of imepitoin. The control group received an initial dosage of 2 mg/kg phenobarbital twice daily which could also be increased, depending on response, first to 4 mg/kg twice daily, and then to 6 mg/kg twice daily, if required. The 6 mg/kg twice daily dosage represented the "maximum allowed dosage" of phenobarbital. All dosage had to be given for at least two weeks before a dose could be increased depending on response.

For each dosage of study treatment, seizures were considered to be uncontrolled as soon as one of the following scenarios was fulfilled:

- Seizure frequency had not been reduced by more than 50% compared to the baseline. Consequently, the seizures were considered to be uncontrolled if the number of seizures occurring under the dosage exceeded the maximum tolerated number of seizures (Nmax).
- Occurrence of at least one serial seizures event, i.e. at least two generalized seizures within 12 hours.

226 client-owned dogs were randomised to treatment groups, either imepitoin (116) or phenobarbital (110). Approximately 70 breeds, ranging from 0.8 to 15 years of age, and from 5 to 65 kg in weight were included. For the inclusion the following criteria had to be met: newly diagnosed idiopathic epilepsy and at least two generalised seizures within a 6 week baseline assessment period. Additionally the 6 week baseline period needed to be properly and accurately documented.

The following exclusion criteria were applied: Seizures due to other causes than idiopathic epilepsy, partial seizures in its history, status epilepticus in its history, previous anti-epileptic treatment for seizure control at least 4.5 months before inclusion day, history or clinical symptoms of hepatic disease, history or clinical symptoms of renal, cardiac, gastro-intestinal, or other disease which would have exposed the dog to unacceptable risk or compromised the evaluation of the study, body weight <5 kg, pregnancy or lactation.

The following criteria lead to the post-inclusion removal of dogs: Actual number of seizures >Nmax despite administration of the maximum allowable dose level (MADL) of the study treatment, serial seizures events despite administration of the MADL of the study treatment, status epilepticus, non-permitted concomitant treatment (i.e. use of any other anti-epileptic drug); phenobarbital serum concentration ≥ 45 µg/ml, severe adverse event that made further participation impossible, withdrawal of owner consent. Further diagnosis during the course of the study revealed that seizures were not due to idiopathic epilepsy. In this case, the investigator specified the diagnosis.

All dogs included in the study and having received at least one dose of the study treatment formed the Full analysis data set on which the safety was evaluated. The efficacy of the study treatment was evaluated on the Per Protocol Set (PPS) population which included all cases without relevant deviations and staying in the evaluation phase for at least 6 weeks and cases removed earlier than 6 weeks after the start of the evaluation because of uncontrolled seizure although the maximum dosage of the study treatment was reached or because of status epilepticus.

A total of 74 cases (52 in imepitoin group (45%) and 22 (20%) in phenobarbital group) in the Full Analysis dataset (FAS, n=226) were excluded from the Per Protocol dataset (PPS, n=152) population.

Primary efficacy variable was the "monthly seizure frequency". Secondary efficacy variables were "change of monthly seizure frequency versus baseline", "proportion of seizure free dogs", "proportion of dogs showing a seizure frequency reduction of ≥50%", "severity of seizure", "general assessment of the study treatment" and "frequency of status epilepticus".

In this study the non-inferiority of imepitoin to phenobarbital was tested in the per protocol population, and a reduction was shown in the baseline mean seizure frequency 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% confidence interval [-0.928, 0.935].

The secondary endpoint evaluated showed the following results:

- The proportion of dogs showing a reduction of ≥ 50% in monthly seizure frequency during the evaluation phase in comparison to baseline was of 75% (48 dogs out of 64) and 83% (73 dogs out of 88) in the imepitoin and phenobarbital group, respectively.
- The proportion of generalized seizure-free dogs was of 47% (30 dogs) and 58% (51 dogs) in the imepitoin and phenobarbital group, respectively.

Several methodological trial deficiencies were identified:

- The analysis was conducted only on the PPS and not on the FAS. An intent-to-treat (ITT) analysis in all treated dogs should have been performed prior to unblinding.
- A high and unbalanced proportion of animals was excluded (45% and 20% of the enrolled imepitoin group and the phenobarbital group, respectively). The reasons for exclusion were in many cases treatment-related which strongly suggests post-randomisation bias in the analysis.

70% of exclusions were mainly due to two types of exclusion criteria:

- 31% were excluded due to "withdrawal of consent" or "loss to follow up" (15 dogs for imepitoin and 8 for phenobarbital).
- 39% were excluded during evaluation phase because of "treatment scheme errors" (19 dogs for imepitoin, 10 for phenobarbital).

Furthermore, a wide non-inferiority margin was selected (1 seizure per month reduction) compared with a study population baseline seizure frequency of approximately 2.5 seizures per month. Additionally, the upper limit of the confidence interval (0.9354) was very close to the non-inferiority margin.

Given the high and unbalanced proportion of animals excluded (which were in many cases potentially failures to respond to treatment), additional descriptive statistical analyses for the proportion of dogs with a 50% frequency reduction or generalised seizure free dogs post unblinding were performed on all treated dogs during the evaluation phase (re-inclusion of 36 and 14 dogs for Pexion and phenobarbital respectively), showing the following results:

- The proportion of dogs showing a reduction of ≥ 50% in monthly seizure frequency during the evaluation phase in comparison to baseline was of 57% (53 dogs out of 93) and 79% (81 dogs out of 102) in the imepitoin and phenobarbital group, respectively.
- The proportion of generalized seizure-free dogs was of 33% (31 dogs out of 93) and 55% (56 dogs out of 102) in the imepitoin and phenobarbital group, respectively.

The safety of imepitoin was assessed on the basis of the incidence, severity and causal relationship of adverse events during the study, and on serum biochemical parameters regarding hepatic and renal function evaluations before and at the end of study treatment.

The most frequently reported adverse events were somnolence/sedation, polydipsia, polyuria, increased appetite, and hyperactivity. Pexion presented the following advantages in term of safety compared to phenobarbital: fewer adverse events were noted for polyuria (10% vs 91%), polydipsia (14% vs 23%) and marked sedation (14% vs 25%) and the following drawback: more hyperactivity (16% vs 6%).

Differences in the levels of five liver enzymes were found when comparing the two treatment groups. 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.

The CVMP concluded that, although the deficiencies in the pivotal EU non-inferiority trial make interpretation difficult and may indicate an overall lower efficacy for imepitoin compared with phenobarbital, some dogs were well controlled on imepitoin treatment.

Other studies

Studies investigating the development of tolerance and dependence development during chronic administration were included and described in part 3 of this report. These studies were considered supportive for the dose determination/selection which is based on the same model of PTZ seizure in dogs.

Overall conclusion on efficacy

Imepitoin has anticonvulsant activity against electrically and chemically induced seizures in mice and rats in genetic models of epilepsy, in models for partial seizures and in models of absence epilepsy. This activity is based on a low affinity towards benzodiazepine binding site of the $GABA_A$-receptor; a weak inhibition of neuronal calcium channels may contribute to its pharmacological activity.

The effective dose varies between 1 and 100 mg/kg depending on the model in rodents. No tolerance appears in rodents after repeated administration of imepitoin.

The proposed posology of 10 mg to 30 mg imepitoin per kg bw twice daily approximately 12 hours apart, was tested in laboratory studies using a seizure model in dogs and in clinical pilot field studies. The pilot field studies with two follow-up studies were considered only as supportive for the dose selection since the final formulation was not used in these studies which furthermore did not meet the GCP compliance.

Tolerance and dependence development was investigated during chronic administration in the PTZ model. No tolerance development was observed but mild behavioural and muscular signs were observed upon termination of treatment with imepitoin.

A supportive field trial conducted in USA failed to demonstrate the non-inferiority to the positive control product containing primidone which is not approved within the EU. The following adverse events occurred more often in the primidone group: hepatopathy (enzyme elevation) (16% vs 5%), ataxia (13% vs 6%), polydipsia (15% vs 3%), hyperactivity (10% vs 3%), anxiety (9% vs 3%), tachypnoea (6% vs 1%) and disorientation (5% vs 1%). Since a positive control was used in this study which is not approved in the EU, the clinical data of this study was considered only as supportive evidence for the efficacy of this product.

A pivotal EU field trial compared the final formulation of the test product containing imepitoin to a positive control product containing phenobarbital.

In this study the non-inferiority of imepitoin to phenobarbital was tested in the per protocol population, and a reduction was shown in the baseline mean seizure frequency 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% Confidence interval [-0.928, 0.935].

The secondary endpoint evaluated showed the following results:

- The proportion of dogs showing a reduction of ≥ 50% in monthly seizure frequency during the evaluation phase in comparison to baseline was of 75% (48 dogs out of 64) and 83% (73 dogs out of 88) in the imepitoin and phenobarbital group, respectively.
- The proportion of generalized seizure-free dogs was of 47% (30 dogs) and 58% (51 dogs) in the imepitoin and phenobarbital group, respectively.

Several methodological trial deficiencies were identified:

- The applicant conducted the statistical analysis before unblinding only on the per protocol population and not on the intent-to-treat population.
- A high and unbalanced proportion of animals was excluded (45% and 20% of the enrolled imepitoin group and phenobarbital group, respectively). The reasons for exclusion were in many cases treatment-related which strongly suggests post-randomisation bias in the analysis.

The PP analysis is important to test the scientific hypotheses of the trial whereas the ITT analysis is a truer reflection of the field situation. An intent-to-treat (ITT) analysis in all treated dogs should have been performed prior to unblinding.

Furthermore, a wide non-inferiority margin was selected (1 seizure per month reduction) compared with a study population baseline seizure frequency of approximately 2.5 seizures per month.

Additionally, the upper limit of the confidence interval (0.9354) was very close to the non-inferiority margin.

Given the high and unbalanced proportion of animals excluded (which were in many cases potentially failures to respond to treatment), additional descriptive statistical analyses for the proportion of dogs with a 50% frequency reduction or generalised seizure free dogs post unblinding were performed on all treated dogs during the evaluation phase (re-inclusion of 36 and 14 dogs for Pexion and phenobarbital respectively), showing the following results:

- The proportion of dogs showing a reduction of ≥ 50% in monthly seizure frequency during the evaluation phase in comparison to baseline was of 57% (53 dogs out of 93) and 79% (81 dogs out of 102) in the imepitoin and phenobarbital group, respectively
- The proportion of generalized seizure-free dogs was of 33% (31 dogs out of 93) and 55% (56 dogs out of 102) in the imepitoin and phenobarbital group, respectively.

The most frequently reported adverse events were somnolence/sedation, polydipsia, polyuria, increased appetite, and hyperactivity. Pexion presented the following advantages in term of safety compared to Phenobarbital: fewer adverse events were noted for less polyuria (10% vs 19%), polydipsia (14% vs 23%) and marked sedation (14% vs 25%), and the following drawback: more hyperactivity (16% vs 6%).

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.

Though efficacy may not be complete, imepitoin is considered a suitable treatment option in some dogs because of its safety profile. Therefore, the proposed indication for Pexion is: "For the reduction of the frequency of generalised seizures due to idiopathic epilepsy in dogs for use after careful evaluation of alternative treatment options".

Part 5 – Benefit risk assessment

Introduction

Pexion 100 and 400 mg tablets are tablets containing either 100 mg or 400 mg imepitoin and are intended for oral administration in dogs.

The tablets are white, oblong, half-scored ones with embedded logo "I 01" (100 mg) or "I 02" (400 mg) on one side which can be divided into equal halves. The product is presented in HDPE bottles with child-resistant closures and a desiccant canister.

The proposed indication is: 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 recommended treatment dose is 10 mg/kg to 30 mg/kg twice a day.

The application is submitted as a full (Article 12(3)) application. Imepitoin is considered a new active substance which was never authorised before neither as a human nor as a veterinary pharmaceutical product.

Benefit assessment

Direct therapeutic benefit

Imepitoin is a centrally acting antiepileptic substance with anticonvulsant properties. It acts partially at the benzodiazepine binding site of the $GABA_A$-receptor with low affinity. Imepitoin potentiates the amplitude of $GABA_A$- receptor-mediated inhibitory effects on the neurons, and thereby prevents seizures. Moreover, a weak inhibition of neuronal calcium channels may contribute to its anticonvulsive properties.

Pexion has shown to reduce the monthly seizure frequency although the deficiencies in the pivotal EU non-inferiority trial make interpretation difficult and may indicate an overall lower efficacy for imepitoin compared with the standard treatment. Nevertheless, some dogs were well controlled on imepitoin treatment.

The adverse events shown by Pexion in clinical field trials were less pronounced compared to the standard treatment. Furthermore, biochemical parameters on hepatic function showed no alteration with increasing dose of imepitoin, in contrast to the standard treatment.

Additional benefits

Pexion contains the novel active substance, imepitoin. It has a different mode of action than other active substances currently authorised for the treatment of epilepsy in the EU. Pexion increases the range of available treatment possibilities for idiopathic epilepsy.

Additionally, it was shown that adverse events such as sedation and polyuria and polydipsia were less frequent for Pexion when compared to standard treatment. These findings illustrate a potential safety benefit of Pexion in comparison with the standard treatment.

Risk assessment

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

The following mild and generally transient adverse reactions have been observed in pre-clinical and clinical studies (in order of decreasing frequency): polyphagia, also hyperactivity, polyuria, polydipsia, somnolence, hypersalivation, emesis, ataxia, apathy, diarrhoea, prolapsed nictitating membrane, decreased sight and sensitivity to sound.

The efficacy and safety of the product has not been tested in dogs weighing less than 5 kg or in dogs with safety concerns such as renal, liver, cardiac, gastrointestinal or other disease. The safety of the veterinary medicinal product has not been established during pregnancy and lactation in dogs.

The toxicity tests indicate a low margin of safety of imepitoin in dogs.

The product is safe for the user and for the environment, when used as recommended.

Risk management or mitigation measures

Appropriate sentences are included in the SPC and product information to prevent risks for the target animal. The product should not be used in dogs weighing less than 5 kg or in dogs with severely impaired hepatic, renal or severe cardiovascular disorders. The use of Pexion in these dogs should be done according to the benefit-risk assessment by the responsible veterinarian.

Pexion is not recommended in male breeding dogs or in female dogs during pregnancy and lactation. Appropriate warning sentences are included in section 4.10 for the case of repeated overdose.

Appropriate sentences are included in the SPC and product information to prevent risks the user, especially for children. The child tamper-proof screw closures decrease significantly the risk of accidental ingestion by a child.

Standard safety advice for safe disposal is included in the SPC.

Evaluation of the benefit risk balance

The formulation and manufacture of Pexion, well described, and specifications set should ensure that product of consistent quality will be produced.

The safety of imepitoin to target animals, user and the environment was characterised satisfactorily. Appropriate warnings are included in the SPC.

Pexion increases the range of available treatment possibilities for idiopathic epilepsy and presents a potential safety benefit in comparison with the standard treatment, phenobarbital.

The CVMP concluded that, although the deficiencies in the pivotal EU non-inferiority trial make interpretation difficult and may indicate an overall lower efficacy of imepitoin compared with phenobarbital, some dogs were well controlled on imepitoin treatment. The pharmacological response to imepitoin may vary and efficacy may not be complete. Nevertheless, imepitoin is considered to be a suitable treatment option in some dogs considering in particular its safety profile.

Conclusion on benefit risk balance

The overall benefit risk balance of Pexion for the use in dogs for the reduction of generalised seizures (frequency) is positive.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Pexion is approvable.

The quality, safety and efficacy of Pexion are considered to be in accordance with the requirements of Directive 2001/82/EC, as amended. The overall benefit/risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/CVMP/734636/2012
Veterinary Medicine and Product Data Management

Divergent position to the CVMP opinion on Pexion (EMEA/V/C/002543)

Introduction

Epilepsy is a brain disorder that causes dogs to have sudden uncontrolled recurring physical attacks. Idiopathic epilepsy is the result of functional cerebral disturbances for which there is no underlying cause other than a genetic predisposition.

There are several basic mechanisms thought to be involved in the action of antiepileptic medicinal products. First, these medicinal products may induce a functional block of voltage-gated sodium channels (phenytoin, carbamazepine). Second, they can directly or indirectly enhance inhibitory GABAergic transmission (benzodiazepines, barbiturates including phenobarbital and primidone have this effect). Third, they can inhibit excitatory glutamatergic neurotransmission (topiramate) and, fourth, modulate calcium ion channels (gabapentin). Imepitoin is a new active substance acting as a partial agonist of GABA-receptor and also as a weak inhibitor of neuronal calcium channels.

Although many potential therapeutic agents are available with various modes of actions, few antiepileptic medicinal products are authorised or simply suitable for use in the dog. This is almost invariably because the pharmacokinetics of the products have very short elimination half-lives in dogs. This means that it is difficult or impossible to maintain therapeutic plasma concentration even if the drug is given several times a day (Chandler, 2006).

The most commonly used antiepileptic medicinal products in dogs are phenobarbital and potassium bromide, both of which have a long history in the treatment of both human and canine epilepsy.

Phenobarbital (a barbiturate) is currently the drug of first choice in dogs. High level of phenobarbital (>32 microg/ml) may cause hepatotoxicity. Side effects are mainly lethargy, polyuria, polydipsia and polyphagia.

Pexion contains imepitoin as the active ingredient. Pexion proposed indication is "an antiepileptic agent 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 route of administration is oral use.

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Efficacy data documentation

Pharmacokinetic data

Pharmacokinetic studies indicate that imepitoin is well absorbed (> 92%) after oral administration.

Imepitoin is extensively metabolised prior to elimination and is rapidly cleared from blood with a short elimination half-life of approximately 1.5 to 2 hours.

Pilot field studies

Several pilot studies performed with a non final formulation did not enable to conclude that Imepitoin products may be non-inferior to Phenobarbital treatment.

The use as an add-on therapy has only been investigated in seventeen dogs in an open and uncontrolled trial using a non-final formulation.

US field trial

A supportive clinical field study was conducted in USA to evaluate the safety and the efficacy of the product in dogs with idiopathic epilepsy. In this trial the final formulation of imepitoin (Pexion) was compared to a product containing primidone. Imepitoin and primidone were shown to be effective in reducing seizures by ≥50% compared with baseline in more than 60% of the animals (62.4% and 84.2 % for imepitoin and primidone, respectively). This trial failed to demonstrate non-inferiority of imepitoin to primidone.

EU field trial

A pivotal EU field trial compared the final formulation of the test product containing imepitoin to a positive control product containing phenobarbital.

Efficacy results in per protocol population (PPS) (152 dogs):

In this study the non-inferiority of imepitoin to phenobarbital was tested in the per protocol population, and a reduction was shown in the baseline mean seizure frequency 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 secondary endpoint evaluated for 12 weeks during evaluation phase showed the following results:

- The proportion of dogs showing a reduction of ≥ 50% in monthly seizure frequency during the evaluation phase in comparison to baseline was lower in imepitoin group (75%, 48 /64) than in phenobarbital group (83%, 73/88).
- The proportion of generalized seizure-free dogs was lower in imepitoin group (47%, 30/64) than in phenobarbital group (58%, 51/88).

Several methodological trial deficiencies were identified:

- A high and unbalanced proportion of animals were excluded (45% and 20 % of the enrolled imepitoin and phenobarbital groups, respectively). The reasons for exclusion were, in many cases, treatment-related which strongly suggests post-randomisation bias in the analysis.
- The applicant conducted the statistical analysis before unblinding only on the per protocol population and not on the intent-to-treat population. An intent-to-treat (ITT) analysis in all treated dogs should have been performed prior to unblinding.

- A wide non-inferiority margin was selected (1 seizure per month reduction) compared with a study population baseline seizure frequency of approximately 2.5 seizures per month. Additionally, the upper limit of the confidence interval (0.9354) was very close to the non-inferiority margin.

These major methodological trial deficiencies did not enable the CVMP members signing the divergent opinion to consider the results of the study from the calculations made in the per protocol population only as robust.

To assess if the numerous excluded dogs may have been "non responders" to treatment and know if their exclusions may have biased the results, additional statistical analyses post unblinding were performed by the Applicant on all treated dogs during the evaluation phase (P2 population):

Efficacy results P2 population (195 dogs):

- The proportion of dogs showing a reduction of ≥ 50% in monthly seizure frequency during the evaluation phase in comparison to baseline was lower in imepitoin group (57%, 53/93) than in phenobarbital group (79%, 81/102).
- The proportion of generalized seizure-free dogs was lower in imepitoin group (33%, 31/93) than in phenobarbital group (55%, 56/102).

The calculation made in the P2 population showed that the exclusion of many dogs during the evaluation phase biased the results. In the opinion of the CVMP members signing the divergent opinion, the calculations made when including all treated dogs during evaluation phase show that Pexion may have a lower efficacy than phenobarbital.

As part of the CVMP assessment, an additional analysis was performed on the cases where an increase of seizures was observed. This showed that Pexion may induce more increase in seizure frequency than phenobarbital:

In P2 population (=PPS + dogs excluded during evaluation phase) (195 dogs), 26% of dogs experienced an increase in seizure frequency in Imepitoin group vs 11% for phenobarbital.

In the excluded dogs population (64 dogs), these figures rise to 60% of dogs with increased seizure frequency for Pexion vs. 14 % for phenobarbital. It would not be assumed that the natural disease progression were different in the two groups.

Therefore, these results may be due to the lack of efficacy in stemming the natural progression of the disease or due to an intrinsic effect of the product modifying the excitatory threshold in sick animals.

Conclusion on efficacy data:

The efficacy data indicate an overall lower efficacy for imepitoin compared with phenobarbital because:

- Several pilot studies performed with a non final formulation did not enable to conclude Imepitoin products may be non inferior to phenobarbital treatment.
- The US field trial study failed to demonstrate non-inferiority of imepitoin to primidone. In this study, Pexion efficacy was lower than primidone (62.4% of dogs with more than 50 % of reduction in seizure frequency vs 84.2 % for imepitoin and primidone, respectively).
- The EU field trial study failed to demonstrate non-inferiority of imepitoin to phenobarbital. In this study, Pexion efficacy was lower than phenobarbital when calculation were made including all treated dogs during evaluation phase (57% of dogs with more than 50 % of reduction in seizure frequency vs 79 % for imepitoin and phenobarbital, respectively). It is acknowledged that a rate of exclusions above 10-20% after randomisation bias a treatment comparison and hinds the

extrapolation or "generalisability" of the results to the target population (Schulz KF et al., 2002, Moher D. et al, 2010, Fergusson D. et al., 2002).

- Furthermore, no placebo-controlled trial was provided which would have allowed measuring the treatment effect of imepitoin. Moreover the treatment effect of the positive reference product was lower than expected (only 1.3 reduction of mean seizure frequency compared to 4 seizures in Boothe et al., 2012). The comparison to a reference product which does not perform as well as expected lowers the validity of the comparison.

This lower efficacy of imepitoin may be due to the main mode of action of imepitoin (which binds with low affinity at the benzodiazepine binding site of the GABA-receptor) or to the pharmacokinetic features of the molecule (the drug's half life is short, so the therapeutic plasma concentration may not be maintained at a sufficient level between two administrations).

The CVMP included a number of clinical study results in the SPC in order to aid the attending veterinarian allow him or her to make a proper benefit/risk analysis prior to treating with Pexion; however, it is felt that these results, as they pertain to the per protocol groups do not adequately reflect what the veterinarian would observe in the field. The intent to treat population, in general give more pertinent information of efficacy in all treated dogs; however, these results were not made available.

In terms of labelled indications for use and potential use in the field, the use as a second line treatment has not been tested. The use as an add-on therapy also has not been sufficiently investigated.

Safety data documentation

Toxicology

A large number of studies were presented characterising the repeated dose toxicity profile of imepitoin in the target and non-target species (dogs, rats, monkeys). These studies showed that the safety margin of imepitoin in dogs is low (LOAEL = 31.6 mg/kg in one study) and close to the recommended dose (10 to 30 mg/kg BID). The results were very homogenous, no matter which target species. Adverse effects were often similar and mainly due to pharmacological activities of imepitoin. This product was originally proposed for use as a human medicinal product. Hence, some toxicity studies were performed in dogs.

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Tolerance in target safety

The following adverse effects were observed in the tolerance study (a target animal safety study performed expressly as part of the veterinary medicinal product development) and in the clinical studies: prolapsed nictitating membrane, decreased activity, vomiting, hypersalivation, diarrhoea, decrease of body weight, ataxia, disorientation with disturbances of equilibrium or co-ordination, hyperactivity and restlessness, decreased sight and sensitivity to sound, polyphagia, increase in creatinine and cholesterol levels.

Tolerance data from field trials

In the US field trial, the following adverse events occurred more often in the primidone group than in the imepitoin group: hepatopathy (enzyme elevation) (16% vs 5%), ataxia (13 % vs 6%), polydipsia (14% vs 3%), hyperactivity (10% vs 3%), anxiety (9% vs 3%), tachypnoea (6% vs 1%), and disorientation (5% vs 1%).

In the pivotal European field trial comparing the efficacy of imepitoin to phenobarbital, 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. The most frequently reported adverse events were somnolence/sedation, polydipsia, polyuria, increased appetite, and hyperactivity. Less adverse reactions were observed in imepitoin treated dogs compared to Phenobarbital treated dogs: less sedation (14% vs 25 %), less polyuria (10% vs 19%) and polydipsia (14% vs 23%).

However, it should not be concluded that Pexion presents a clear advantage over Phenobarbital since the clinical trials were not designed to demonstrate the improved safety of the product. The absence of non-inferiority in efficacy may have been acceptable only if the safety benefit had been demonstrated by using a second primary endpoint based on a safety variable. This case is mentioned in the human guideline on the choice of the non inferiority margin (EMEA/CPMP/EWP/2158/99).

Conclusion on safety data:

The safety data indicate a trend for a better safety profile of Pexion in comparison to phenobarbital, but a definitive improved tolerance has not been demonstrated.
It is hypothesized that the mechanisms behind Pexion's lesser impact possibly resulting in better tolerance for many of the adverse events than phenobarbital are the same as those responsible for lower efficacy.

Benefit risk assessment

Pexion promises to the attending veterinarian to increase the range of available treatment possibilities for idiopathic epilepsy; however, such a promise has not been backed up by demonstrated efficacy.

It is acknowledged that the safety data indicate a trend for a better safety profile of Pexion in comparison to Phenobarbital; however, a definitive improved tolerance has not been demonstrated and the importance of this, where efficacy is not demonstrated, and worsening is seen in some dogs, is questioned.

The efficacy data indicate an overall lower efficacy for imepitoin compared with Phenobarbital. In some cases, as just stated, treated animals get worse. Consequently, the veterinarian is not felt to be in a good position to perform a discerning benefit-risk analysis prior to treatment. Additional studies should be provided to elucidate the mechanism of action and indicate more clearly how this product should be used in the field.

The overall benefit risk balance of Pexion for the use in dogs for the reduction of generalized seizures frequency, the primary parameter of interest, is, for those CVMP members who have signed the divergent opinion, considered to be negative.

[redacted]

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