28 May 2026
EMADOC-1700519818-2099149
Veterinary Medicines Division

Targeted signal management (TSM) for Phenobarbital in cats and dogs

1. Background

Phenobarbital is the first choice for treatment and long-term management of epileptic seizures in dogs and cats. There are many veterinary medicinal products (VMPs) authorised through many different procedures in the EU/EEA, and both the history and interconnectedness of these products are complicated. The Union Product Database (UPD) lists 205 VMPs belonging to 9 different Marketing Authorisation Holders (MAHs), which can be crudely grouped based on procedure numbers and MAHs into 9 VMPs (with 12 different trade names). VMPs belonging to the ATCvet code for phenobarbital (QN03AA02) have a 'due date' for the annual statement submission in the IRIS platform by the end of November.

All VMPs on the market today, containing phenobarbital alone, are oral formulations, and all are authorised for dogs only. Despite this fact, phenobarbital is still recommended by veterinarians as the first choice for treatment of epileptic seizures in cats as well under 'Use of VMPs outside the terms of the marketing authorisation in non-food-producing animal species', often known as cascade use (Article 112 of EU 2019/6).

In November 2023 one MAH (Desitin) submitted a signal regarding a delayed hypersensitivity syndrome observed in both dogs and cats known as 'anticonvulsant hypersensitivity syndrome' (AHS) and sometimes referred to as "pseudolymphoma". The signal was submitted for three of the MAH's VMPs ('Luminal vet', 'Luminaletten vet' and 'Epirepress') with a proposal for close monitoring. An analysis performed by the national competent authority (NCA) (Danish Medicines Agency) responsible for evaluating the signal (from here on referred to as Lead Member State (LMS)), concluded that the signal was not unique to one specific product, rather, it was most likely related to the active substance, and a TSM was therefore considered warranted. Furthermore, during the evaluation, the LMS identified three other potential signals for the active substance, which were not included (in a harmonised way) in the different SPCs of products belonging to the ATC code for Phenobarbital (QN03AA02). These three signals ('Pancreatitis' in dogs, 'Elevated serum lipids' in dogs and 'Elevated liver enzymes' in dogs) have been included in this TSM. The original signal of AHS in dogs and cats was separated into one signal for dogs and one for cats, leading to a total of five signals included in the TSM.

The TSM proposal was endorsed by the Pharmacovigilance Working Party (PhVWP-V) at the meeting on 26-27 March 2024 and the Coordination Group for Mutual Recognition and Decentralised Procedures for Veterinary Medicinal Products (CMDv) at the meeting on 25-26 April 2024.

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The proposed "Lead Member State" for this specific targeted signal management, as mandated by Regulation (EU) 2019/6 Article 81(4), was the Danish Medicines Agency (DKMA).

1.1. Objectives

The objective of the TSM procedure was to collect data, knowledge and comments from all involved MAHs and coordinate and perform further analysis, if necessary, to determine if amendment to the PI is needed regarding any of the above-described signals. Any amendment to the PI recommended at the end of this procedure would be recommended for all VMPs under the same ATCvet code, as all signals appear to pertain to the active substance phenobarbital.

In order to avoid duplication of work, and unnecessary administrative burden for all parties involved, the aim was to evaluate all five signals together under the same TSM procedure.

1.2. Methodology

After endorsement by PhVWP-V and CMDv, a communication was sent to the MAHs involved, notifying them of the TSM procedure and asking for submission of relevant data and comments in IRIS. The communication regarding all five signals was combined in one notification letter. Information on the TSM procedure was published on the EMA website with no reference to the trade names of the VMPs involved (the ATCvet code QN03AA02 will be used instead to describe these VMPs in a more generic manner).

Regarding the signal on 'Anticonvulsant hypersensitivity syndrome', all MAHs were asked to check their internal databases for reports corresponding to the described clinical image and provide a list of relevant reports, if any (with EVV-case numbers where relevant) including reports classified as non-serious prior to 28 January 2022.

An additional notification letter was sent to the MAH that submitted the original signal on 'Anticonvulsant hypersensitivity syndrome' to thank them for their submission and analysis and ask them to submit a list of EVV-case numbers for the original cases in their analysis where relevant (since this was not included in their original signal submission). This was communicated to the MAH in IRIS.

For the signal on 'Anticonvulsant hypersensitivity syndrome', further analysis of the received data was performed. All the adverse event reports were collected, and all data assessed with regards to causality. A search of available literature was also performed.

For the signals on 'Pancreatitis', 'Elevated serum lipids' and 'Elevated liver enzymes' comments and data received from the MAHs were collected, analysed and assessed further where necessary.

With regards to all signals, all MAHs were asked to comment on the signals and the potential risk minimisation measures under consideration. Comments from the MAHs were provided through the network signal in IRIS.

After commencement of the analysis, the results were presented to the PhVWP-V and adopted by CMDv.

Overview of involved MAHs and VMPs

Involved MAHs	Involved VMPs	Country of Registration
Dechra	Phenoleptil Phenoral	BE, CZ, SE, AT, IT, EL, PT, SI, UK (Northern Ireland), DK, FI, FR, DE, HU, IS, IE, LU, NO, PL, SK, ES NL
CH Generics Limited	Phenototyl	LT
Destin	Luminal Luminaletten Epirepress	DE DE AT, BE, DK, ES, NL, PT, SE
CP-Pharma	Phenotab (Epibarb)	NL, BE, PT, UK (Northern Ireland), AT, PL, IT, ES, HU, IE, DE SE, DK, FI
Domes Pharma-LOC	Soliphen Phenovet	DE, IT, BE, UK (Northern Ireland), NL, FR, AT, PT, ES, LU DE, UK, AT, IE
Vetoquinol	Epiphen Barbivet	UK FI
Pannon VetPharma	Epityl	HU
Chanelle Medical Limited	Epityl	BE, FI, DK, PL, SE, CZ, FR, PT, UK (Northern Ireland), AT, CY, LU, IT, IE, SI, ES, DE, NL, BG EL (NATL)
Le VET	Phenoleptil	LU (same procedure numbers as Dechra Phenoleptil)

2. Signal assessments

2.1. 'Anticonvulsant Hypersensitivity Syndrome' in cats

One MAH (Desitin) submitted a signal for close monitoring in November 2023 regarding a delayed hypersensitivity syndrome observed in both dogs and cats known as 'anticonvulsant hypersensitivity syndrome' (AHS) (also occasionally referred to as "pseudolymphoma"). The signal from the MAH involved 12 cases concerning cats from both spontaneous adverse event reports and literature.

The initial analysis of adverse event reports in EudraVigilance Veterinary (EVV) Data Warehouse (DWH) revealed 8 additional reports of 'pseudolymphoma' in cats as well as 12 cases with skin symptoms alone.

Based on the analysis of the submitted signal evaluation report, and the additional reports found in EVV DWH concerning other VMPs, the following clinical image appeared for cats:

Lymphadenopathy (enlargement of lymph nodes) affecting more than one lymph node and appearing between 1 week and up to 6 months after treatment start with phenobarbital. Sometimes associated with oedema, itchy and/or necrotic, and/or ulcerative and/or erythematous skin lesions, lethargy/apathy, decreased appetite and/or anaemia or thrombocytopaenia. Cases with no lymphadenopathy, but only severe skin lesion associated with pruritus, necrotic lesions, erythema, ulcerations and hair loss starting within the same timeframe were also seen and could be connected.

The clinical image appears serious and many of the cases include a positive dechallenge, and there are unfortunately also several deaths related to the syndrome in cats.

There is a wide variety of products involved in the reports, and some of the literature reports do not state which VMP was used or whether human formulations of phenobarbital were used. Furthermore, similar reactions to phenobarbital and other aromatic anticonvulsant medications are known and well described in humans (e.g. 'Pseudolymphoma', 'DRESS syndrome', 'Steven-Johnsons syndrome', 'Toxic epidermal necrolysis' and more). This leads to conclude that the observed problem is not unique to one specific product, and considering the many different VMPs and MAHs, a coordinated effort to investigate this issue further was considered warranted. Further collection and creation of a complete overview of the data was considered necessary to reach a conclusion for the signal on 'Anticonvulsive hypersensitivity syndrome' in cats.

None of the currently marketed phenobarbital-product are indicated for use in cats. Nevertheless, phenobarbital is considered the first-line choice of treatment of epileptic seizures in cats, and is therefore widely used off-label under use of VMPs outside the terms of the marketing authorisation, i.e. cascade use (Article 112 of EU 2019/6).

LMS conclusion:

Following their own reviews the MAHs found that the data available to them was insufficient to conclude on a causal association with AHS in cats. However, three MAHs were supportive of keeping the signal under close monitoring, with one MAH recommending to keep it focused on 'lymphadenopathy' in cats, while another focused on "hypersensitivity reaction" and the third proposed to widen the search beyond just AHS. Only one MAH appeared to have submitted an update to the signal in 2025.

Up until the data lock point of the request to MAHs (30 June 2024), the LMS and MAHs identified a total of 63 cases of potential AHS in cats. Causality assessment of these 63 cases varies but at least 37 cases, including a total of 11 well-described cases from scientific literature, are considered strongly supportive of the signal. Many of the identified cases included a positive dechallenge which strongly supports a causal association.

The LMS later performed an updated analysis of EVV DWH of cases reported between 01 November 2023 and up until 31 December 2025 and identified nine additional cases which may represent AHS; two cases showed lymphadenopathy, two cases had skin lesions with other systemic symptoms, while the remaining five cases concerned only skin lesions. Three of the nine cases are considered strong. In total, there are 72 cases of which 40 are considered strong.

As acknowledged by all MAHs, similar hypersensitivity reactions/severe cutaneous adverse reactions (SCARs) are listed for humans in the SmPC of human phenobarbital. The occurrence of AHS with phenobarbital thus fits in the pharmacological-toxicological profile of the active substance. Since the mechanism in humans is well-established, a similar process can be believed to occur in cats.

Therefore, the LMS finds that the evidence supports a causal association between phenobarbital and AHS (AHS as defined above) in cats. This opinion is based on the severity of the adverse event and that the mechanism is well established in humans and therefore fits the pharmacological-toxicological profile of the active substance. Additionally, there are several cases in cats reporting positive dechallenges. The clinical image described in the cases appears serious, with many cases associated with lymphadenopathy or 'pseudolymphoma' where cats run the risk of misdiagnosis of cancer with potentially fatal outcome. However, it is acknowledged that it is likely a very rare event, as is also the case in humans. The frequency of reports seems to be very rare with only few reports per product. The LMS therefore finds that placing AHS in cats under close monitoring is not likely to generate additional relevant information, as the expected number of submitted reports is likely to be very low.

Awareness of this risk is important for veterinarians to avoid unnecessary diagnostic procedures and treatments with potent drugs e.g. chemotherapy and/or antibiotics, and to avoid potential unnecessary euthanasia, as the symptoms of AHS in cats often mimic cancerous lesions. Veterinarians would instead be enabled to attempt a dechallenge in suspect cases, since prompt discontinuation of the suspected culprit drug is the most important therapeutic measure.

PhVWP-V recommendation:

The PhVWP-V found that the evidence supports a likely causal association between anticonvulsant hypersensitivity syndrome in cats and treatment with phenobarbital. The adverse event is considered serious and preventable, and therefore it is recommended to inform prescribers about this risk, taking into consideration that the adverse event occurs in a non-target species following use outside the terms of the marketing authorisation.

The PhVWP-V recommends direct communication to prescribers, to be disseminated by the individual NCAs of the concerned member states as they see fit. Following the conclusion of this TSM-procedure, a communication plan will be established by the PhVWP-V in accordance with the VGVP module on pharmacovigilance communication.

'Anticonvulsant hypersensitivity syndrome' (AHS) in dogs

One MAH (Desitin) submitted a signal for close monitoring in November 2023 regarding a delayed hypersensitivity syndrome observed in both dogs and cats known as 'anticonvulsant hypersensitivity syndrome' (AHS). The signal from the MAH involved approximately 12 dogs (one literature report was unclear regarding the number of dogs) from both spontaneous adverse event reports and literature.

The initial analysis of adverse event reports in EVV DWH revealed 7 additional reports with a similar clinical presentation for dogs.

Based on the analysis of the submitted signal evaluation report, and the additional reports found in EVV DWH concerning other VMPs, the following clinical image appeared for dogs:

Erosive, necrotising, crusty skin lesions and/or lymphadenopathy (enlargement of lymph nodes) affecting more than one lymph node. Symptoms appear between 1 week and up to 6 months after treatment start with phenobarbital and are sometimes associated with lethargy.

The clinical image appears less serious for dogs compared to cats, but many of the cases include a positive dechallenge.

Furthermore, similar reactions to phenobarbital and other aromatic anticonvulsant medications are known and well described in humans (e.g. 'Pseudolymphoma', 'DRESS syndrome', 'Steven-Johnsons syndrome', 'Toxic epidermal necrolysis' and more). This leads to conclude that the observed problem is not unique to one specific product, and considering the many different VMPs and MAHs, a coordinated effort to investigate this issue further was considered warranted. Further collection and creation of a complete overview of the data was considered necessary to reach a conclusion for the signal on 'Anticonvulsive hypersensitivity syndrome' in dogs.

LMS Conclusion:

Initially, there was no consensus between the MAHs who responded to the TSM regarding the outcome of the signal; two MAHs proposed close monitoring, while one MAH proposed to close the signal. One MAH did not provide a conclusion. Upon review of the draft version of this assessment report, two MAHs agreed to close monitoring of this signal.

The LMS performed an updated search of EVV DWH from 01 November 2023 to 31 December 2025 and identified 19 additional cases of potential AHS in dogs from this period. Two of the cases were

considered probably related to phenobarbital treatment, while nine were considered possibly related. Overall, three cases were considered strongly supportive of the signal.

In total, 91 unique potential cases of AHS in dogs have been identified from spontaneous reports and literature. 55 of these cases are considered supportive of AHS in dogs to some extent. However, compared to AHS in cats, the events appear less severe in dogs and concern mostly skin reactions. There are also fewer strongly supportive cases in dogs compared to cats – only 17 cases were considered strongly supportive by the LMS. Furthermore, the reported events are less uniform in their presentation, and the syndrome therefore appears less well defined in dogs compared to cats. As skin reactions are the most reported clinical sign in dogs with suspected AHS it may also be difficult to differentiate from other skin disorders and particularly from Superficial Necrolytic Dermatitis, which is already listed in SPC section 3.6 of some phenobarbital products. A few of the presented cases also mention suspicion of Erythema Multiforme.

Hypersensitivity reactions/ SCARs similar to those observed in dogs are well described in humans and therefore, the LMS finds that AHS in dogs fits with the pharmacological-toxicological profile of the active substance. Since the mechanism in humans is well-established, a similar mechanism could be behind the observed reactions in dogs.

The LMS finds that the current evidence is not sufficient to establish a causal association between treatment with phenobarbital and 'Anticonvulsive hypersensitivity syndrome' in dogs with any certainty, although the suspicion of a causal association still stands. The LMS proposes to keep AHS in dogs under close monitoring for all VMPs belonging to the ATCvet code for phenobarbital (QN03AA02). The MAHs should monitor only for severe skin reactions and for cases with lymphadenopathy and/or pseudolymphoma as described in the updated criteria outlined below. They should submit yearly updates to the signal under close monitoring, although they only need to submit an updated signal report if they identify new cases that fit the criteria of AHS AND these cases are considered supportive of a causal association.

PhVWP-V recommendation:

The PhVWP-V requests the MAHs to keep AHS in dogs under close monitoring for all VMPs belonging to the ATCvet code for phenobarbital (QN03AA02). The MAHs should monitor for severe skin reactions and for cases with lymphadenopathy and/or pseudolymphoma as described in the updated criteria:

Dogs: Serious and/or widespread, erosive, necrotising, crusty skin lesions and/or lymphadenopathy (enlargement of lymph nodes) affecting more than one lymph node. Symptoms appear between 1 week and up to 6 months after treatment start with phenobarbital; sometimes associated with lethargy.

It is recommended to monitor the cases reporting the PT 'lymphadenopathy' as well as all cases of 'skin and appendages disorder' and 'immune system disorders' at SOC-level to screen for cases that fit the criteria.

All MAHs of products containing phenobarbital (ATCvet code QN03AA02) should submit a signal for close monitoring at the time of the next annual statement. Since AHS is not a VeDDRA term, it is recommended to submit the signal with the VeDDRA PTs 'skin disorder NOS', 'lymphadenopathy' and 'hypersensitivity reaction'. For the signals submitted in 2026, any new cases or literature, that fit the updated criteria of AHS and are considered supportive of a causal association, identified since the data lock point of the last submission should be provided (i.e. either since the data lock point for this submission (30/06/2024) or any later submissions on the topic). A full signal assessment is not required.

Signals under close monitoring are expected to be updated yearly in IRIS. However, to lower the administrative burden associated with the signal, an updated signal assessment report should only be submitted if new cases, that fit the updated criteria of AHS, and are considered supportive of a causal association, are identified. If no such cases have been identified, it is sufficient to submit a signal with a statement that monitoring in relation to this active-substance level signal has been carried out, no new supportive cases were identified and refer to this TSM assessment report.

2.2. 'Pancreatitis' in dogs:

Pancreatitis, whether acute or chronic, is a serious medical condition causing significant suffering in affected individuals and carries a significant risk of death.

Pancreatitis was not included in the adverse events section of any of the product informations for any of the phenobarbital-products approved at the time of initiation of this TSM. A warning of an increased risk of pancreatitis when combining phenobarbital with potassium bromide is included under the section for drug interactions in around half of the authorised products.

Literature:

Evidence in literature supported a causal association between monotherapy with phenobarbital and an increased risk of pancreatitis as well as the current knowledge that combined therapy of phenobarbital with potassium bromide further increases this risk:

- Gaskill et. al. 2000: 0.3% of dogs on phenobarbital experience pancreatitis, while it is 10% if combined with bromide.
- Steine et. al. 2008: 6.7% of dogs treated with phenobarbital has an elevated Specific Canine Pancreatic Lipase (Spec CPLi) value.
- Kluger et al 2008: 16% of treated dogs had a history of pancreatitis (most on monotherapy, some combined with potassium bromide)
- Albarracin et. al. 2015: Spec CPLi is increased by 6.8% of dogs, but only 0.6% show symptoms of clinical acute severe pancreatitis. CRP values are shown to be higher in dogs treated with phenobarbital or phenobarbital in combination with potassium bromide than dogs treated with potassium bromide alone. A correlation is shown between an increase in ALP, ALT, triglycerides and Spec CPLi values.
- Charalambous et. al. 2016: Review article of 43 studies on phenobarbital - 20% of the studies report pancreatitis as a non-dose dependent adverse event.
- Flegel 2016 (consensus from WSAVA congress): 'Pancreatitis' is stated as an adverse event of phenobarbital.
- Bhatti et. al 2015 (consensus statement): 'Pancreatitis' is stated as an adverse event.
- DeRisio and Platt 2014: 'Pancreatitis' is stated as a known adverse event, linked to elevated serum lipids.
- Hess et al. 1999: The authors evaluated 70 cases of acute pancreatitis and found epilepsy to be a risk factor. The authors speculate whether anticonvulsant therapy may be the underlying cause for this association.
- Bizzeti et al. 2006: The authors evaluated 14 dogs with idiopathic epilepsy treated with either phenobarbital monotherapy or phenobarbital in combination with potassium bromide and found the prevalence of acute pancreatitis to be 14.3% for monotherapy and 42.8% for combination-therapy.

- Cridge et al. 2022: Lists the association of phenobarbital and potassium bromide among drugs considered to be a risk factor for the development of pancreatitis in dogs.
- Podell et al. 1993: Also referenced by DeRisio and Platt (2014), they suggest a mechanism of phenobarbital-induced pancreatitis through polyphagia, which is a well-known adverse event linked to phenobarbital.

Analysis of Eudravigilance data:

The DWH was checked with a data lock point of 31/12/2025 using the ATC code, and the current ROR(-) is 1.65 for elevated pancreatic enzymes and 3.56 for pancreatitis and the total number of reports on pancreatitis and elevated pancreatic enzymes (unique cases when combined) in dogs are 77, of which only 25 report concurrent use of potassium bromide (e.g. Libromide, Solibrom etc.).

Newly authorised phenobarbital products:

In the first quarter of 2025, two new veterinary medicinal products containing phenobarbital were approved on bibliographical applications - Phenosan and Phenocoat. These products were not part of this TSM procedure.

The LMS notes that 'Pancreatitis' is included in SPC section 3.6 of both products with a frequency of "uncommon".

LMS Conclusion:

Following their own reviews of data, there was no consensus between the MAHs regarding this signal. Two MAHs did not find the evidence sufficient to support a causal association, while another MAH proposed to update section 3.6 to include pancreatitis. The remaining MAHs who provided data, did not provide an overall conclusion. Following review of the draft version of this report, two additional MAHs supported inclusion of pancreatitis in the SPCs as recommended below, while the remaining did not provide comments.

Considering the complete body of data from both the initial and follow-up evaluation by the LMS, as well as the additional data received from the MAHs, it is the opinion of the LMS that a causal association between phenobarbital and pancreatitis is a reasonable possibility also without concurrent use of potassium bromide. From the literature, pancreatitis appears to be a risk even with phenobarbital monotherapy, which is further supported by the fact that the majority of cases of pancreatitis and elevated pancreatic enzymes in both DWH and the cases reported by the different MAHs, do not report concurrent use of potassium bromide. It is acknowledged, that the risk is even higher when phenobarbital is combined with potassium bromide, but the LMS does not consider this to negate that there is a risk with monotherapy as well.

PhVWP-V recommendation:

The PhVWP-V recommends inclusion of 'Pancreatitis' in the adverse events table in SPC section 3.6 in the frequency category "uncommon", with a footnote under the table; "*The risk of pancreatitis increases further with combined treatment with potassium bromide*".

The current warning regarding this interaction should also remain in section 3.8 "Interaction with other medicinal products and other forms of phenobarbital"; "*Concurrent use with potassium bromide increases the risk of pancreatitis*." The products that currently do not include such a warning in SPC section 3.8 should therefore update the SPCs to include it.

2.3. 'Elevated serum lipids' in dogs

Chronically elevated serum lipids have been linked to an increased risk of pancreatitis in dogs, as well as other serious conditions such as hypertension, stroke, and heart disease. The correlation is stronger for elevated triglycerides compared to cholesterol.

Literature:
Evidence supporting causality between treatment with phenobarbital and elevated serum lipids were found in scientific literature (see below):

- Kluger et. al. 2008: Dogs treated long-term with phenobarbital may develop hypertriglyceridaemia. 33% of epileptic dogs in the study had increased levels of triglycerides.
- Albarracin et. al. 2015: Triglycerides increased in 38,3% of dogs treated with phenobarbital. Cholesterol increased by 17%. A correlation between an increase in ALT, ALP, triglycerides and Spec CPLi was found.
- Xenoulis and Steiner 2015: Mentions phenobarbital as a cause of hyperlipidaemia.
- De Risio and Platt 2014: Mentions increased serum lipids as an adverse event and links it to pancreatitis.
- Bhatti et. al 2015 (consensus statement): 'Elevated serum lipids' is stated as an adverse event.
- Balana et a. 2023: Reported on a case of hypertriglyceridaemia in relation to phenobarbitone-induced hepatotoxicity in a dog.
- Foster et. al. (2000) reported severe hypertriglyceridaemia in 2 of 12 healthy dogs treated with phenobarbital (16.7%).
- Müller et al. (2000) reported elevated cholesterol in 3 of 12 (25%) healthy dogs after 27 weeks of treatment with phenobarbital.
    - Gieger et al. (2000) followed up the dogs from Müller's study and found that cholesterol decreased following discontinuation of phenobarbital.
- Aitken et al. (2003) found elevated cholesterol in 7 of 95 treated dogs (7.4%) in their study.
- Contrary to these findings, Chauvet et al. (1995) found that mean concentrations of cholesterol decreased in 5 dogs during treatment.

Analysis of Eudravigilance data:

The DWH was checked using a data lock point of 31/12/2025 using the ATC code, and the ROR(-) was 11.36 for elevated serum lipids and the total number of reports on elevated serum lipids in dogs are 123 of which the majority report elevated cholesterol.

Newly authorised phenobarbital products:

In the first quarter of 2025, two new veterinary medicinal products containing phenobarbital were approved on bibliographical applications - Phenosan and Phenocoat. These products were not part of this TSM procedure.

The LMS notes that 'Elevated serum lipids' is included in SPC section 3.6 of both products with a frequency of "uncommon".

LMS Conclusion:

Following their reviews, there was no consensus between the MAHs who responded to the TSM. Three MAHs refuted the signal, while one MAH proposed to update the product information in sections 3.5 and 3.6. However, upon reviewing the draft version of this AR, two of the MAHs who initially refuted the signal expressed support for the recommendation as provided below.

The LMS acknowledges the conflicting evidence regarding elevated serum lipids. Several studies have found a causal association between treatment with phenobarbital, both with and without concomitant potassium bromide, and elevated serum lipids. However, there are also studies linking this elevation to liver damage, introducing the possibility of a secondary effect. There are also other factors to take into account such as Body Condition Score (BCS) and sampling technique, as well as the clinical relevance of elevated cholesterol in comparison to elevated triglycerides.

Taking all the presented data into consideration and further considering the recent inclusion of elevated serum lipids in section 3.6 of two newly authorised phenobarbital-products, it is the opinion of the LMS that the evidence supports a causal association.

PhVWP-V recommendation:

The PhVWP-V recommends inclusion of a specific recommendation in SPC section 3.5 to monitor serum lipids (including cholesterol and triglycerides) along with the other monitoring recommendations mentioned. Proposed text:

"Elevated serum lipids may be seen with phenobarbital therapy in dogs. Since chronically elevated serum lipids have been linked to an increased risk of pancreatitis in dogs, serum lipids (including cholesterol and triglycerides) should be periodically monitored".

2.4. 'Elevated liver enzymes' in dogs (and 'Elevated alkalic phosphatase' and 'Elevated aspartate transferase')

The ability of phenobarbital to induce an increase in serum concentration of liver enzymes is one of the most well researched adverse events of this active substance. At the initiation of the TSM, the term was already included in section 4.5/3.5 of all products, where it was referred to as an adverse event, albeit it was only included in the adverse events section (3.6) of one approved product information at the time (Barbivet). Hepatic toxicosis was already included in the adverse events section of all products.

The ability of clinicians to be able to differentiate between a 'benign' increase in liver enzymes and hepatic toxicosis is considered essential to avoid withdrawing important treatment from dogs who only experience an increase in serum levels of liver enzymes with no clinical signs of actual toxicosis. Having both hepatic toxicosis and elevated liver enzymes appear in section 3.6, while also providing updated recommendations on monitoring in section 3.5, would increase awareness, patient safety, and align the product information with current scientific knowledge. The causal effect of an elevation of liver enzymes during phenobarbital treatment is broadly supported by scientific literature, also in cases with no evidence of toxicosis.

Literature:

The causal effect of an elevation of liver enzymes during phenobarbital treatment is overwhelmingly supported by scientific literature, also in cases with no evidence of toxicosis – the references are too numerous to list in full. Reputable literature such as "Plumb's veterinary drug handbook" also mentions elevation of liver enzymes as a well-known adverse event, only rarely correlated to hepatic toxicosis, and provides guidance of interpretation of levels in relation to when to suspect hepatic toxicosis or not.

Another textbook, "Fundamentals of Veterinary Clinical Pathology" (Stockham and Scott), also mentions phenobarbital as a common cause of drug-induced elevation of liver enzymes.

One MAH cited an unknown clinical study which found a frequency of elevated liver enzymes of 4.2% corresponding to a frequency of "common".

A non-exhaustive review of selected available literature provided by one of the MAHs found evidence in support of a causal association between treatment with phenobarbital and elevated serum alkaline phosphatate (ALP) and serum alanine aminotransferase (ALT) but not serum gamma-glutamyl transferase (GGT), which did increase from baseline in the different studies, but not above normal level, nor with aspartate aminotransferase (AST) which was only studied in one article (Müller et al. 2000) where no difference had been found in 12 healthy dogs. One study (Gaskill et al. 2005) found no significant increase in histological signs of liver injury in phenobarbital-treated dogs with elevated liver enzymes in serum. Additionally, the MAH found further textbooks (in addition to Plumb's) referencing that serum bilirubin, ammonia, fasted bile acids and ultrasonographic and histologic evaluation of the liver may be more useful for investigation of liver injury in dogs treated with phenobarbital, which was also reflected in the summary for a new phenobarbital product recently approved in the US by FDA.

Analysis of Eudravigilance data:

The DWH was checked with a data lock point of 31/12/2025 using the ATC code, and the ROR(-) was 6.05 for elevated liver enzymes, 12.63 for elevated aspartate aminotransferase (AST) and 11.54 for elevated serum alkaline phosphatate (ALP). The total number of reports were 380, 84 and 446 respectively (likely with some overlapping reports).

Newly authorised phenobarbital products:

In the first quarter of 2025, two new veterinary medicinal products containing phenobarbital were approved on bibliographical applications - Phenosan and Phenocoat. These products were not part of this TSM procedure.

The LMS notes that both 'Hepatic toxicosis' and 'Elevated liver enzymes' are included in SPC section 3.6 of both products with a frequency of "uncommon" and "very common" respectively.

LMS Conclusion:

There is general consensus between the responding MAHs, that there is evidence of a causal association between treatment with phenobarbital and an increase in serum liver enzymes without hepatotoxicity. The LMS finds that this aspect should be reflected clearly in the product information, and that guidance should be offered to distinguish between situations where a dose-decrease or discontinuation is needed versus more benign states of elevated liver enzymes, which may not require immediate action.

PhVWP-V recommendation:

The PhVWP-V recommends inclusion of 'Elevated liver enzymes' in the adverse events table in section 3.6 in the frequency category "common", with a footnote stating; "*May not necessarily be indicative of hepatic dysfunction. See also section 3.5.*"

Furthermore, it is recommended to update the recommendations given in section 3.5:

"*Before beginning the treatment, monitoring of hepatic parameters should be performed. The chance of hepatotoxic side effects can be diminished or delayed using an effective dose that is as low as possible. Monitoring of hepatic parameters is recommended in case of a prolonged therapy. It is recommended to assess the clinical pathology of the patient 2-3 weeks after start of treatment and afterwards every 4-6 months, e.g. measurement of serum alkaline phosphatase (ALP) and alanine*

aminotransferase (ALT), bilirubin, serum aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and bile acids. It is important to know that the effects of hypoxia can cause increased levels of hepatic enzymes after a seizure. Phenobarbital may increase the activity of ALP and ALT. These may demonstrate non-pathological changes, but could also represent hepatotoxicity, so liver function tests are recommended. Increased ALP and/or ALT values may not always require a dose reduction of phenobarbital if serum AST, GGT, bile acids and bilirubin are in the normal range. If serum ALT or ALP are moderately elevated or the animal shows clinical signs of hepatic dysfunction, dose reduction or discontinuation should be considered in all cases."

Annex 1 – References:

Annex 1.1 – General references

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