SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 29 November 2018

doi: 10.2903/j.efsa.2019.5542

Assessment of the application for renewal of authorisation of Lantharenol® (lanthanum carbonate octahydrate) for cats

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Abstract

Lantharenol® is a feed additive consisting of lanthanum carbonate octahydrate. It is currently authorised as a zootechnical additive (decrease in phosphorous excretion via urine) for cats; this opinion concerns the renewal of the authorisation. In 2007, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) adopted an opinion on the safety and efficacy of Lantharenol® as a feed additive for cats. The applicant has provided data demonstrating that the additive complies with the conditions of authorisation. The available evidence, including the results of the post-market monitoring plan, confirms that the use of Lantharenol® in cat food at the maximum authorised concentration of 7.5 g/kg of complete feed is safe for cats. In the absence of new data, the FEEDAP Panel reiterates its previous conclusion that Lantharenol® does not pose a risk by inhalation and is not an irritant to skin or eye and not a dermal sensitiser. The FEEDAP Panel considers that there is no need for a continuation of a specific post-market monitoring plan.

Keywords: zootechnical additives, other zootechnical additives, Lantharenol®, lanthanum carbonate octahydrate, cat, renewal

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Question number: EFSA-Q-2017-00288

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Legal note: Relevant information or parts of this scientific output have been blackened in accordance with the European Commission decision on the confidentiality requests formulated by the applicant. The full output has been shared with the European Commission, EU Member States and the applicant.

Acknowledgements: The Panel wishes to thank the following for the support provided to this scientific output (in alphabetical order of the last name): Agnese Balzani, Rosella Brozzi, Jaume Galobart and Lucilla Gregoretti.

Suggested citation: EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Bampidis V, Azimonti G, Bastos ML, Christensen H, Dusemund B, Kouba M, Kos Durjava M, López-Alonso M, López Puente S, Marcon F, Mayo B, Pechová A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen R, Chesson A, Gropp J, Martelli G, Renshaw D, López-Gálvez G and Mantovani A, 2019. Scientific Opinion on the assessment of the application for renewal of authorisation of Lantharenol® (lanthanum carbonate octahydrate) for cats. EFSA Journal 2019;17(1):5542, 9 pp. https://doi.org/10.2903/j.efsa.2019.5542

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 14(1) of that Regulation lays down that an application for renewal shall be sent to the Commission at the latest one year before the expiry date of the authorisation.

The European Commission received a request from Bayer Healthcare AG[2] for renewal of the authorisation of Lantharenol® (lanthanum carbonate octahydrate), when used as a feed additive for cats (category: 'zootechnical additive', functional group: 'other zootechnical additives').

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 14(1) (renewal of the authorisation). The particulars and documents in support of the application were considered valid by EFSA as of 11 April 2017.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of Lantharenol® (lanthanum carbonate octahydrate), when used under the proposed conditions of use (see Section 3.1.3).

1.2. Interpretation of the Terms of Reference

The application for renewal of the authorisation does not include a proposal for amending or supplementing the conditions of the original authorisation that would have an impact on the efficacy of the additive; therefore, efficacy is not assessed. The present opinion will focus only on the safety aspects.

1.3. Additional information

The FEEDAP Panel adopted in 2007 an opinion on the safety and efficacy of this product as a zootechnical additive for cats (EFSA, 2007).

The additive (lanthanum carbonate octahydrate, Lantharenol®) is authorised for cats.[3]

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[4] in support of the authorisation request for the use of Lantharenol® (lanthanum carbonate octahydrate) as a feed additive. The technical dossier was prepared following the provisions of Article 14 of Regulation (EC) No 1831/2003, Regulation (EC) No 429/2008[5] and the applicable EFSA guidance documents.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers and other scientific reports to deliver the present output.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment are valid and applicable for the current application.[6]

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2] Bayer HealthCare AG Animal Health Division 51368 Leverkusen Germany.
[3] Commission Regulation (EC) No 163/2008 of 22 February 2008 concerning an authorisation of the preparation Lanthanum carbonate octahydrate (Lantharenol) as a feed additive. OJ L 50, 23.2.2008, p. 3.
[4] FEED dossier reference: FAD-2017-0013.
[5] Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.
[6] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2011-0021.pdf

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of Lantharenol® (lanthanum carbonate octahydrate) is in line with the principles laid down in Regulation (EC) No 429/2008 and the Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2013).

3. Assessment

This assessment regards the renewal of the authorisation of the product Lantharenol® (≥ 85% lanthanum carbonate octahydrate) as a zootechnical additive, functional group 'other zootechnical additives', to be used in feedingstuffs for cats at the minimum and maximum content of 1,500 and 7,000 mg/kg complete feed, respectively. The specific intended effect under the authorisation granted is: 'decrease in phosphorous excretion via urine'.

3.1. Characterisation

3.1.1. Characterisation of the additive

The additive Lantharenol® contains lanthanum carbonate octahydrate (Chemical Abstracts Service (CAS) No 6487–39–4, molecular formula $La_2(CO_3)_3 \cdot 8H_2O$ and molecular weight 601.9 Da) as the active substance.

The applicant stated that no changes have been introduced in the manufacturing process of the additive since the original authorisation.[redacted]

The applicant declared that the additive contains ≥ 85% of lanthanum carbonate octahydrate, with the remainder being loosely bound water. The specifications of the additive, regarding the content of the main constituents are: lanthanum 43–49%, carbonate 27–33% and ash 44–58%. The analysis of three batches of the additive showed that Lantharenol® meets those specifications: lanthanum 45%, carbonate 31.3% (range 31–32%) and ash 48.3% (range 48–49%). Analysis of heavy metals and other impurities in the same batches also met the specifications (all results in mg/kg): fluoride 22.6 (range 22–23); arsenic < 2; cadmium < 1; chromium < 2; lead < 1; mercury < 0.2.[8,9] Analysis of dioxins in three other batches of Lantharenol® showed an average content of 0.585 ng WHO-PCDD/F-TEQ/kg additive (range: 0.576–0.600).[10]

The applicant also conducted analysis of Lantharenol® for microbiological contamination (total aerobic count, yeasts and moulds and *Escherichia coli*) in three batches of the additive. Lanthanum carbonate octahydrate is an inorganic material and is not expected to support microbiological growth. The results of the analysis confirmed this expectation.

It is noted that the analyses were performed on batches of the additive older than one year from the date of the submission of the current application (analyses dated of 2014)[11]; the applicant explained that fresh batches were not available for analysis because the additive is not currently being manufactured or marketed.[12]

The additive Lantharenol® (lanthanum carbonate octahydrate) is a white crystalline powder. The applicant submitted the same analysis for particle size distribution and dusting potential already provided in the precedent dossier.[13,14] These data were evaluated and reported in the earlier FEEDAP Panel opinion on Lantharenol® for cats (EFSA, 2007).

[redacted]

[8] Technical Dossier/Section II/Annex II_2.

[9] The applicant clarified that the symbol '<' in all cases indicates that the findings were below the specification limit; however, in the view of the FEEDAP Panel, uncertainty remains regarding the LOQ/LOD of the analytical method. Technical Dossier/Supplementary Information.

[10] Technical Dossier/Section II/Annex II_13.

[11] The FEEDAP Guidance for the renewal of authorisations states that: 'Recent (not older than one year from the date of submission of the application) analytical data from at least three batches for the composition of the additive and for the purity should be provided'.

[12] Technical Dossier/Supplementary Information/Annex 1.

[13] Technical Dossier/Section II/Annex II_12.

[14] Technical Dossier/Section II/Annex II_16–17.

3.1.2. Stability and homogeneity

In the current application, the applicant provided data already submitted in the previous application – which will not be re-assessed in the current scientific opinion – and additional studies aiming to support the stability of the additive in premixtures. [redacted]

3.1.3. Conditions of use

Lantharenol® is a feed additive that acts as an intestinal phosphate binder in cats. The duration of administration is continuous. Lantharenol® should be incorporated into cat feed to achieve a concentration of 1.5–7.5 g/kg of complete feed.

The current authorising Regulation indicates under *Other provisions* that:

- the additive is for use in adult cats,
- the recommended dose of inclusion in moist feed with 20–25% dry matter content is 340–2,100 mg/kg and
- the simultaneous use of Lantharenol® with high phosphorus feeds should be avoided.

3.2. Safety

Since the use of the additive is only for cats, safety for consumers and the environment is out of the scope of this scientific opinion. Therefore, the safety evaluation considers only the safety for cats and the safety for the users.

The applicant performed a literature search in order to provide evidence that in the light of the current knowledge the additive remains safe for cats and users under the approved conditions of use.[16] The scientific databases consulted were PubMed, Science Direct and Google Scholar; the search period covered from January 2008 to October 2017. The keywords used were: 'Lantharenol cat', 'Lantharenol human patient', 'Lantharenol user', 'Lantharenol environment', 'Lantharenol safety', 'Lantharenol safety cat', 'Lantharenol safety environment' and 'Renalzin'. A total of 444 scientific papers were retrieved. Only four of the articles were considered potentially relevant, all related to the safety of Lantharenol for cats.

The FEEDAP Panel notes that the search made by the applicant considered only the trade name of the additive and not the chemical name of the active substance.

3.2.1. Safety for the target species

In the previous opinion on Lantharenol®, the FEEDAP Panel reported that 'Based on the data from the two tolerance studies provided in which no negative effects were seen after supplementing the diet with at least a 10x overdose, the FEEDAP Panel concludes that Lantharenol® is safe for cats under the conditions of use proposed' (EFSA, 2007).

To support the safety of the additive for the target species, the applicant has provided new data in the form of results of the post-market monitoring (PMM) plan foreseen in the authorisation and the outcome of a literature search.

3.2.1.1. Results of the post-market monitoring plan

In its previous assessment, the FEEDAP Panel recommended a PMM plan for Lantharenol® (EFSA, 2007). This monitoring aimed to examine any consequence of the chronic exposure of cats to the additive. A PMM plan was subsequently imposed in the authorising Regulation. The results of the PMM have been submitted in the current dossier and summarised below.

The Marketing Authorisation Holder (MAH) has performed continuous PMM, pharmacovigilance and evaluations of the benefit–risk balance of Renalzin™, a complementary feed for particular nutritional

[redacted]
[16] Technical Dossier/Supplementary Information.

purposes, containing Lantharenol® at 14% w/w. Lantharenol® was first placed on the European Union (EU) market in October 2008. The FEEDAP Panel agrees that the PMM data on Renalzin™ are relevant to Lantharenol®. Two Global Periodic Safety Update Report (PSURs) were prepared by the MAH covering the following periods: 12/9/2008 to 30/9/2009 (PSUR1)[17] and 1/10/2009 to 31/5/2012 (PSUR2).[18] The line listings for adverse events reported after the Data Lock Point of the last PSUR[19] which covered the period 1/6/2012 to 31/12/2016 were also included in the technical dossier. The reports covered the monitoring of the product not only in the countries of the European Economic area but also in non-EEA and worldwide. Furthermore, they covered also incidences in non-target species as well as off-label use of the product.

In total, there were 29 non-serious adverse events and 9 serious adverse events reported since the authorisation was granted, taking into account both on-label and off-label uses in target species. Considering the volume of Renalzin™ sold and the estimated number of treatments administered, the incidence of adverse events reported in the target species was 0.0003% each for the periods covered by PSUR1 and PSUR2. Thus, the worldwide incidence of adverse events following the use of Renalzin™ in cats is low.

The most frequently affected system organ class reported in the target species was digestive tract disorder, with the reported effects including inappetence, diarrhoea and vomiting. Non-specific systemic disorders were also reported (exicosis, dehydration, depression, fever). The next most common organ systems affected were the cardiovascular and respiratory systems. Neurological disorders (nystagmus and circling) in connection with hypersalivation were reported in one other cat. However, as the reported signs were nearly all common non-specific events, and in cats suffering from renal disease, a product–disorder relationship was unclassifiable in the majority of cases. For all cases of death and euthanasia (8 cats in total worldwide; occurred only in the period covered by PSUR2, a product–disorder relationship was described by the MAH as unclassifiable or unlikely.

The incidence of adverse events (including decreased intake of water for drinking and vomiting in dogs) reported in non-target species since the authorisation was granted was also low: three non-serious and one serious, involving four animals in total, thus indicating that adverse effects were rare.

In the context of the PMM, the MAH conducted literature reviews quarterly since when Lantharenol® was first authorised.[16] The applicant provided the list of search terms used in these literature searches.[20] The literature search found no reports indicating safety concerns to the target species or the user following the use of Lantharenol®.

3.2.1.2. Results of the literature search

From the literature search performed (see also paragraph under Section 3.2), only four scientific papers were chosen as being potentially relevant to the safety assessment. The FEEDAP Panel considered these four papers and found that one of them (Schmidt et al., 2012) – in an unpublished form – had been already assessed in the previous application. The other three papers (DiBartola, 2010; Thom et al., 2013; Bernachon et al., 2014) did not provide any relevant additional information on the safety of the product when used for cats. Consequently, there is no new information available that would require the FEEDAP Panel to change its conclusions on target animal safety made in the previous Opinion on Lantharenol (EFSA, 2007).

3.2.1.3. Conclusions on safety for the target species

The available evidence, based on the results of an extensive PMM showing a very low rate of reported adverse effects in cats and on the outcome of a limited literature search, allowed the FEEDAP Panel to confirm that the use of Lantharenol® in cat food at the maximum authorised concentration of 7.5 g/kg of complete feed is safe for the target animals.

[17] Technical Dossier/Section III/Annex_III_1.
[18] Technical Dossier/Section III/Annex_III_2.
[19] Technical Dossier/Section III/Annex_III_3.
[20] Lantharenol® was used as a keyword in the search along with: Abuse, Adverse Drug Reaction, Adverse Effect, Adverse Event, Adverse Experience, Adverse Reaction, Carcinogen, Cytotoxicity, Drug Interaction, Drug Safety, Efficacy, Environment, Extra-Label Use, Fatal Outcome, Interaction, Intoxication, Lactation Maximum Residue Limit, Mic, Minimal Inhibitory Limit, Misuse, MRL, Mutagen, Off-Label Use, Overdose, Pharmacodynamics, Pharmacokinetic, Pharmacology, Pharmacovigilance, Poison, Pregnant, Residue, Resistant, Safety, Side Effect, Suicide, Teratogen, Tolerance, Toxicity, Transmission Of Infectious Agent, Unlicensed Use, Withdrawal Period.

3.2.2. Safety for the user

The previous opinion on Lantharenol® reported that 'Although the inhalation exposure did lead to some persistent effects in the lung of exposed rats which was not fully explained, the dusting studies indicate that user exposure via this route will not occur to any significant extent. The substance is not an irritant to skin or eye and is not a dermal sensitizer, is negative in genotoxicity tests and shows no evidence of systemic effects in a 90-day study. On the basis of all this information, there is no indication for any specific protective measures for handling this product either in a domestic or commercial environment' (EFSA, 2007).

Even if not specifically required in the PMM, the applicant also monitored the possible adverse effects of the use of the product in humans (in the context of user safety). No reported adverse effects in humans were collected in the period from 12/9/2008 to 31/12/2016.

In the absence of any new information, the FEEDAP Panel reiterates its previous conclusion on the safety for the users.

3.3. Post-market monitoring

In the light of the results obtained from the PMM during the 10-year post-authorisation period, the FEEDAP Panel considers that there is no need for a continuation of a specific PMM plan.

4. Conclusions

The applicant has provided data demonstrating that the additive complies with the conditions of authorisation.

The available evidence, including the results of the PMM plan, confirms that the use of Lantharenol® in cat food at the maximum authorised concentration of 7.5 g/kg of complete feed is safe for cats.

The FEEDAP Panel reiterates its previous conclusion that Lantharenol® does not pose a risk by inhalation and is not an irritant to skin or eye and not a dermal sensitiser.

The FEEDAP Panel considers that there is no need for a continuation of a specific PMM plan.

Documentation provided to EFSA

1) Lantharenol® Feed Additive containing lanthanum carbonate octahydrate. February 2017. Submitted by Bayer HealthCare AG Animal Health Division Germany.
2) Lantharenol® Feed Additive containing lanthanum carbonate octahydrate. Supplementary information. October 2017. Submitted by Bayer HealthCare AG Animal Health Division Germany.
3) Comments from Member States.

Chronology

Date	Event
7/3/2017	Dossier received by EFSA
12/4/2017	Reception mandate from the European Commission
6/6/2017	Application validated by EFSA – Start of the scientific assessment
13/7/2017	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterisation, safety*
6/9/2017	Comments received from Member States
10/10/2017	Reception of supplementary information from the applicant - Scientific assessment re-started
29/11/2018	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2013. Guidance on the renewal of the authorisation of feed additives. EFSA Journal 2013;11(10):3431, 8 pp. https://doi.org/10.2903/j.efsa.2013.3431

Schmidt BH, Dirbusch U, Delport PC, Gropp JM and van der Staay FJ, 2012. Tolerability and efficacy of the intestinal phosphate binder Lantharenol® in cats. BMC Veterinary Research, 8, 14.

Thom N, Er E and Reinacher M, 2013. Nonuraemic nonfatal idiopathic calciphylaxis in a kitten. Veterinary Dermatology, 24, 547–e131.

Abbreviations

CAS	Chemical Abstracts Service
EURL	European Union Reference Laboratory
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
LOD	limit of detection
LOQ	limit of quantification
MAH	Marketing Authorisation Holder
PCDD/F	polychlorinated dibenzo-*p*-dioxins/dibenzofurans
PMM	post-market monitoring
PSUR	Periodic Safety Update Report
TEQ	toxic equivalent
WHO	World Health Organization