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Assessment of the application for renewal of authorisation of pyridoxine hydrochloride (vitamin B₆) as a feed additive for all animal species

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Abstract

Following a request from the European Commission, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the assessment of the application for renewal of authorisation of pyridoxine hydrochloride (vitamin B₆) produced by chemical synthesis as a feed additive for all animal species. The applicant has provided data demonstrating that the additive in the market complies with the conditions of the authorisation. The FEEDAP Panel confirms that the use of pyridoxine hydrochloride under the current authorised conditions of use is safe for the target species, the consumers and the environment. Pyridoxine hydrochloride is non-irritant to skin and eyes and is not a skin sensitiser. It may cause photosensitisation. In the absence of inhalation toxicity studies, adverse effects in the respiratory tract cannot be fully excluded. There is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

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Keywords: nutritional additive, vitamin B₆, pyridoxine hydrochloride, renewal, safety

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Table of contents

| | |
|---|---|
| Abstract..... | 1 |
| 1. Introduction..... | 4 |
| 1.1. Background and Terms of Reference..... | 4 |
| 1.2. Additional information..... | 4 |
| 2. Data and methodologies..... | 5 |
| 2.1. Data..... | 5 |
| 2.2. Methodologies..... | 5 |
| 3. Assessment..... | 5 |
| 3.1. Characterisation..... | 5 |
| 3.1.1. Characterisation of the active substance/additive..... | 5 |
| 3.1.2. Conditions of use..... | 6 |
| 3.2. Safety..... | 6 |
| 3.2.1. Reassessment of consumer exposure..... | 7 |
| 3.2.2. Conclusions on safety..... | 7 |
| 3.3. Efficacy..... | 7 |
| 3.4. Post-market monitoring..... | 7 |
| 4. Conclusions..... | 8 |
| 5. Documentation as provided to EFSA/Chronology..... | 8 |
| References..... | 8 |
| Abbreviations..... | 9 |

1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003¹ 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 DSM Nutritional Products² for the renewal of the authorisation of vitamin B₆ (pyridoxine hydrochloride), when used as a feed additive for all animal species (category: nutritional additives; functional group: vitamins, provitamins and chemically well-defined substances having a similar effect).

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). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 10 June 2020.

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 pyridoxine hydrochloride (vitamin B₆), when used under the proposed conditions of use (see Section 3.1.3).

1.2. Additional information

The EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) issued two opinions on the safety and efficacy of vitamin B₆, in the form of pyridoxine hydrochloride, when used as a feed additive for all animal species (EFSA FEEDAP Panel, 2010, 2011).

Vitamin B₆, in the form of pyridoxine hydrochloride, is currently authorised as a nutritional additive for all animal species (3a831).³

Pyridoxine hydrochloride is described in the European Pharmacopoeia 10.0 (PhEur), monograph 0245 (PhEur, 2020).⁴

The Scientific Committee for Food (SCF) established a tolerable upper intake level (UL) for vitamin B₆ of 25 mg/day for adults (SCF, 2000). The EFSA Panel on Dietetic Products, Nutrition and Allergy issued an opinion on dietary reference values for vitamin B₆ (EFSA NDA Panel, 2016).

Pyridoxine hydrochloride is authorised for use in food,⁵ for use in food for nutritional purposes,⁶ in the manufacture of food supplements,⁷ for use in cosmetics as antistatic, hair conditioning and skin conditioning ingredient⁸ and as a veterinary medicinal product.^{9,10}

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 DSM Nutritional Products Ltd, represented in the EU by DSM Nutritional Products Sp. z o.o., Tarczyńska 113, 96-320 Mszczonów, Poland.

³ Commission Regulation (EU) No 515/2011 of 25 May 2011 concerning the authorisation of vitamin B₆ as a feed additive for all animal species, OJ L 138, 26.5.2011, p. 40–42.

⁴ Technical dossier/Section II/Annex II_3_PhEur_0245.

⁵ Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods, OJ L 404, 30.12.2006.

⁶ Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009, OJ L 181, 29.6.2013, p. 35.

⁷ Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2001 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51.

⁸ Commission Decision of 9 February 2006 amending Decision 96/335/EC establishing an inventory and a common nomenclature of ingredients employed in cosmetic products (2006/257/EC). OJ L 97, 5.4.2006, p. 1.

⁹ Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. OJ L 15, 20.1.2010, p. 1.

¹⁰ Commission Regulation (EC) No 997/1999 of 11 May 1999 amending Annexes I, II and III of Council Regulation (EEC) No 2377/90 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin. OJ L 122, 12.5.1999, p. 24.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier¹¹ in support of the authorisation request for the use of the vitamin B₆ (pyridoxine hydrochloride) as a feed additive.

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.¹²

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of vitamin B₆ (pyridoxine hydrochloride) is in line with the principles laid down in Regulation (EC) No 429/2008¹³ and the relevant guidance document: Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2013) and the Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017).

3. Assessment

Vitamin B₆ in the form of pyridoxine hydrochloride (purity > 98.5%) is currently authorised as a feed additive without defining a maximum content for use in feed and water for drinking in all animal species.

This assessment regards the renewal of the authorisation of pyridoxine hydrochloride, when used as a nutritional additive (functional group: vitamins, provitamins and chemically well-defined substances having a similar effect) for all animal species.

3.1. Characterisation

3.1.1. Characterisation of the additive

Pyridoxine hydrochloride is a white to yellowish, fine granular powder. It is soluble in water (~ 200 g/L), ethanol and propanediol, sparingly soluble in acetone and methanol, insoluble in diethyl ether and chloroform. The bulk density (730–800 kg/m³) and the tap density (940–1,050 kg/m³) were determined in six recent batches of vitamin B₆, produced in the two manufacturing sites (three each).¹⁴

Pyridoxine hydrochloride (International Union of Pure and Applied Chemistry (IUPAC) name: 5-hydroxy-6-methylpyridine-3,4-diy) dimethanol hydrochloride) is identified with the Chemical Abstracts service (CAS) number 58-56-0 and the European Inventory of Existing Chemical Substances (EINECS) number 200-386-2. It has a molecular formula C₈H₁₁NO₃·HCl and a molecular mass of 205.6 g/mol.

The additive under assessment is specified to contain ≥ 98.5% pyridoxine hydrochloride and ≤ 0.5% loss on drying.

The product under assessment is obtained by chemical synthesis. The applicant stated that manufacturing process and the composition of the additive have not been modified since the previous authorisation and provided data from recent batches on the composition of the additive to support this statement.

The applicant provided data on the batch-to-batch variation on ten recent batches of the additive manufactured in two different sites.¹⁵ The concentration of pyridoxine hydrochloride was on average 100.1% (range: 99.8–100.3%), loss on drying 0.01% (range: 0–0.1%) and demonstrated compliance with the existing specifications.

¹¹ FEED dossier reference: FAD-2020-0022.

¹² The full report is available on the EURL website: <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2008-0047.pdf>

¹³ 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.

¹⁴ Technical dossier/Section II.

¹⁵ Technical dossier/Section II_Annex_II_04_CoAs1 and Annex_II_05_CoAs2.

Possible impurities listed in the European Pharmacopoeia were also measured in the same batches, namely 6-methyl-1,3-dihydrofuro[3,4-c]pyridine-7-olacetate (impurity A, < 0.05%) and 5-(hydroxymethyl)-2,4-dimethylpyridin-3-ol (impurity B, < 0.05%). The detected amounts of impurities A to B in ten batches were below the limits specified in the European Pharmacopoeia monograph (0.10% and 0.15%, respectively) (European Pharmacopoeia, 2020).

In the same batches, sulfated ash ranged between 0 and 0.03%, lead was < 2 mg/kg, cadmium < 1 mg/kg, mercury < 0.1 mg/kg and arsenic < 3 mg/kg. The content of residual acetone (162–262 mg/kg) was below the corresponding thresholds set by the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) (EMA, 2010). Aflatoxins (B1, B2, G1 and G2), polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F) and dioxin-like polychlorinated biphenyls (PCBs) were below the corresponding limits of quantification (LOQ) in six batches of the additive.¹⁶ The levels of dioxins and the sum of dioxins and dioxin-like-PCBs (upper bond) were calculated to be 0.16 ng WHO-PCDD/F-TEQ/kg and 0.30 ng WHO-PCDD/F-PCB-TEQ/kg, respectively. The concentrations of the undesirable substances analysed do not represent a concern.

The dusting potential (6 batches) was on average 0.87 g/m³ (range: 0.70–1.18 g/m³).¹⁷ Particle size distribution was analysed in the same batches of the additive. The results showed that no particles with diameter < 1 µm were detected. The proportions of particles with diameters < 10, 50 and 100 µm were 1–2%, 4–8% and 14–20%, respectively.

No new data were provided on the stability and homogeneity of the additive other than was already evaluated by EFSA during its previous assessment (EFSA FEEDAP Panel, 2011).

3.1.2. Conditions of use

Vitamin B₆ in the form of pyridoxine hydrochloride (purity > 98.5%) is currently authorised for use in feed and water for drinking without defining a minimum or maximum content.

The authorisation, under other provisions, foresees:

- 1) In the directions for use of the additive and premixture, indicate the storage temperature, storage life and stability to pelleting and in water.
- 2) Vitamin B₆/pyridoxine hydrochloride may be used also via water for drinking.
- 3) For user safety: breathing protection, safety glasses and gloves shall be worn during handling.

The applicant proposes to keep the same conditions of use as authorised.

3.2. Safety

The safety of pyridoxine hydrochloride for the target species, consumers, users and the environment was evaluated in previous opinions (EFSA FEEDAP Panel, 2010, 2011). The FEEDAP Panel concluded that pyridoxine hydrochloride is considered to be safe for all animal species at the commercial use levels and that the use of pyridoxine hydrochloride as a nutritional additive does not give rise to concern for consumers and the environment. Concerning the safety for the user, the Panel concluded that 'pyridoxine hydrochloride is not an irritant to skin and eyes; it is not a skin sensitiser. The Panel notes that pyridoxine hydrochloride may cause photosensitisation. The pyridoxine hydrochloride considered in this opinion has a high dusting potential. A calculation of exposure by inhalation for persons handling the substance in a premixture factory resulted in an intake of 3.1 mg/person/day. Together with exposure by food sources, total exposure would not exceed 60% of the UL. In the absence of inhalation toxicity studies, adverse effects in the respiratory tract cannot be fully excluded'.

The applicant carried out a structured literature search¹⁸ using two databases: PubMed and Scopus. The search was limited to information available since the last authorisation in 2011 until January 2020. The main strings used were: 'pyridoxine hydrochloride OR pyridoxine HCl OR vitamin B₆ OR pyridoxol hydrochloride OR 58-56-0'. Specific subject areas were added in order to restrict the search (such as safety for the different target species [e.g. 'safety for pigs', 'safety for poultry'], safety for user/workers, safety for consumers and safety for the environment). A detailed description of the iterations used and the inclusion/exclusion criteria for the selection were provided.^{17,18}

¹⁶ Technical dossier/Section II/Annex_II_8_Toxins. LOQ aflatoxins 0.5 µg/kg

¹⁷ Technical dossier/Supplementary information August 2020/Vit B6 answer EFSA – Annex.

¹⁸ Technical dossier/Section III/Annex_III_02_Lit_Search.

The search identified 23 publications which were considered relevant for the safety of vitamin B₆. Many of the studies in target animals were designed to determine the optimum level of inclusion of vitamin B₆ in the diet. In most of the studies inclusion of synthetic vitamin B₆ in the diet had no adverse effects on performance parameters of the animals. Some effects of different vitamin B₆ dietary inclusion rates on behaviour, ovulation rate, levels of minerals, egg weight, some haematological or biochemical parameter and immunological parameters were reported, but none of these studies gave rise to safety concerns with the additive under assessment. No publications related to user/worker safety, environmental safety, or residue levels in edible tissues were identified.

3.2.1. Reassessment of consumer exposure

In the previous assessment of the FEEDAP Panel, the overall vitamin B₆ intake was estimated to range between 1.2 and 2.8 mg/day, with food of animal origin contributing for about 50% of the total intake from food sources. The FEEDAP Panel concluded that there was no risk to exceed the UL of 25 mg/day from food sources and that the use of vitamin B₆ as nutritional additive in feed of food producing animal is safe for the consumer (EFSA FEEDAP Panel, 2011).

According to the EFSA opinion on dietary reference values for vitamin B₆ (EFSA NDA Panel, 2016), 'based on data from 13 surveys in nine countries in the EU, average total vitamin B₆ intake ranges across countries from 0.4 to 0.8 mg/day in infants, from 0.9 to 1.3 mg/day in children aged 1 to < 3 years, from 1 to 1.6 mg/day in children aged 3 to < 10 years, and from 1.5 to 2.3 mg/day in children aged 10 to < 18 years. Average total vitamin B₆ intake ranges between 1.4 and 3.1 mg/day in adults (≥ 18 years old)', showing no risk to exceed the UL (SCF, 2000) from food sources.

The NDA Panel opinion also estimated the minimum and maximum percentage contribution of different food groups to vitamin B₆ intake in males and females. Meat (up to 30% in males and 26% in females) and milk products and dairy products (up to 22% in males and 27% in females) were the main food groups contributing to vitamin B₆ intake in all age groups > 3 years of age. The analysis of the 13 dietary surveys in the EFSA Comprehensive European Food Consumption Database (EFSA NDA Panel, 2016) confirmed the conclusions of the previous assessment of the FEEDAP Panel, which showed that food of animal origin represent ~ 50% of total vitamin B₆ intake from food sources (EFSA FEEDAP Panel, 2011).

Therefore, even in the absence of new data on residue levels in edible tissues, the FEEDAP Panel considers that there is no reason to reconsider the conclusions that the use of vitamin B₆ in animal nutrition would not lead to an increase in human consumption above the UL established by the SCF (2000) and considered still valid by EFSA (EFSA NDA Panel, 2016; EFSA, 2018).

3.2.2. Conclusions on safety

Based on the above and the fact that the manufacturing process, the composition of the additive and the conditions of use for the species/categories for which the additive is authorised have not been modified, the Panel considers that there is no evidence to reconsider the conclusions reached in previous assessments. The FEEDAP Panel concludes that vitamin B₆ in the form of pyridoxine hydrochloride remains safe for the target species, the consumer and the environment under the conditions of use currently authorised. Pyridoxine hydrochloride is non-irritant to skin and eyes and is not a skin sensitiser. It may cause photosensitisation. In the absence of inhalation toxicity studies, adverse effects in the respiratory tract cannot be fully excluded.

3.3. Efficacy

The present 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, there is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

3.4. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation¹⁹ and Good Manufacturing Practice.

¹⁹ Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 laying down requirements for feed hygiene. OJ L 268, 8.2.2003, p. 1.

4. Conclusions

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

The FEEDAP Panel concludes pyridoxine hydrochloride (vitamin B₆) remains safe for all the animal species, for the consumers and the environment under the conditions of use currently authorised.

Pyridoxine hydrochloride is non-irritant to skin and eyes and is not a skin sensitiser. It may cause photosensitisation. In the absence of inhalation toxicity studies, adverse effects in the respiratory tract cannot be fully excluded.

There is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

5. Documentation as provided to EFSA/Chronology

| Date | Event |
|------------|---|
| 11/03/2020 | Dossier received by EFSA. Pyridoxine hydrochloride for all animal species. Submitted by DSM Nutritional Products Sp. Z.o.o |
| 06/05/2019 | Reception mandate from the European Commission |
| 10/06/2020 | Application validated by EFSA – Start of the scientific assessment |
| 21/07/2020 | Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: characterisation, safety</i> |
| 28/08/2020 | Reception of supplementary information from the applicant - Scientific assessment re-started |
| 11/09/2020 | Comments received from Member States |
| 30/09/2020 | Opinion adopted by the FEEDAP Panel. End of the Scientific assessment |

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Abbreviations

| | |
|--------------|---|
| CAS | Chemical Abstracts Service |
| EINECS | European Inventory of Existing Chemical Substances |
| EURL | European Union Reference Laboratory |
| FEEDAP Panel | EFSA Panel on Additives and Products or Substances used in Animal Feed |
| IUPAC | International Union of Pure and Applied Chemistry |
| LOQ | limit of quantification |
| NDA Panel | EFSA Panel on Dietetic Products, Nutrition and Allergy |
| PCB | polychlorinated biphenyl |
| PCDD/F | polychlorinated dibenzo- <i>p</i> -dioxin and dibenzofuran |
| SCF | Scientific Committee for Food |
| TEQ | Toxic equivalency factor |
| UL | Upper intake level |
| VICH | International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products |
| WHO | World Health Organization |