SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 3 October 2018

doi: 10.2903/j.efsa.2018.5461

Safety and efficacy of Monteban® G100 (narasin) for ducks for fattening

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Maryline Kouba, Mojca Kos Durjava, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa, Ruud Woutersen, Gabriele Aquilina, Georges Bories, Paul Brantom, Pier Sandro Cocconcelli, Ingrid Halle, Boris Kolar, Pieter Wester, Patrick van Beelen, Orsolya Holczknecht, Maria Vittoria Vettori and Jürgen Gropp

Abstract

Following a request from the European Commission, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety and efficacy of Monteban® G100 for ducks. Monteban® G100, containing narasin, is intended for the prevention of coccidiosis in ducks for fattening at a dose range of 60–70 mg/kg of complete feed. Narasin from Monteban® G100 is safe for ducks for fattening at a level of 70 mg/kg complete feed with a margin of safety of about 4. The FEEDAP Panel assumes that the residues in duck tissues would be of the same magnitude as those measured in the physiologically similar major species, chickens for fattening. The use of Monteban® G100 at a maximum concentration of 70 mg/kg complete feed for ducks for fattening is safe for the consumer without applying a withdrawal period, provided the maximum residue limit (MRL) of 50 μg narasin/kg for all wet tissues would not be exceeded. Monteban® G100 is irritant to the eyes but not to the skin. It has the potential to induce skin sensitisation. The acute systemic toxicity following dermal application is low. Inhalation exposure would pose a risk to persons handling the additive. Narasin, when used as feed additive for ducks for fattening at 70 mg/kg feed, is not expected to pose a risk to the environment. The risk for sediment compartment cannot be assessed. Narasin is not considered to have a bioaccumulation potential. Insufficient data were provided to allow a conclusion on the efficacy of Monteban® G100 in ducks.

Keywords: coccidiostats, narasin, ducks for fattening, safety and efficacy

Requestor: European Commission

Question number: EFSA-Q-2015-00033

Correspondence: feedap@efsa.europa.eu

Panel members: Giovanna Azimonti, Vasileios Bampidis, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Maryline Kouba, Mojca Kos Durjava, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa and Ruud Woutersen.

Acknowledgements: The EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed) wishes to thank the following for the support provided to this scientific output: Jaume Galobart, Lucilla Gregoretti, Gloria López-Gálvez, Jordi Tárres-Call.

Suggested citation: EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 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, Aquilina G, Bories G, Brantom P, Cocconcelli PS, Halle I, Kolar B, Wester P, van Beelen P, Holczknecht O, Vettori MV and Gropp J, 2018. Scientific Opinion on the safety and efficacy of Monteban® G100 (narasin) for ducks for fattening. EFSA Journal 2018;16(11):5461, 12 pp. https://doi.org/10.2903/j.efsa.2018.5461

ISSN: 1831-4732

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

Table of contents

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 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of a feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from Eli Lilly and Company Ltd[2] for authorisation of the product Monteban® G100 (narasin), when used as a feed additive for ducks (category: coccidiostats and histomonostats).

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 4(1) (authorisation of a feed additive or new use of a feed additive). 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 28 April 2015.

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 the product Monteban® G100 (narasin), when used under the proposed conditions of use (see Section 3.1).

1.2. Additional information

The additive Monteban® G100 is a feed additive intended to be used for the control of coccidiosis in ducks. It contains, as the active ingredient, the polyether ionophore narasin which is produced by fermentation of a strain of *Streptomyces* spp. (NRRL 8092).

Monteban® G100 has never been authorised for use in ducks in the European Union. It has been authorised for use in chickens for fattening until August 2014 pursuant to Commission Regulation (EC) No 1464/2004[3] amended by Commission Regulation (EU) No 884/2010[4].

EFSA issued an opinion on the safety and efficacy of Monteban® G100 (EFSA, 2004) for chickens for fattening followed by an opinion on the reduction of the withdrawal time (EFSA FEEDAP Panel, 2010). Recently, Monteban® G100 has been evaluated by the FEEDAP Panel under Article 10(2) of Regulation (EC) No 1831/2003 (EFSA FEEDAP Panel, 2018).

In 2012, the joint FAO/WHO expert committee on food additives evaluated narasin as a veterinary drug (JECFA, 2012).

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[5] in support of the authorisation request for the use of Monteban® G100 as a feed additive. The technical dossier was prepared following the provisions of Article 7 of Regulation (EC) No 1831/2003 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, other scientific reports and experts' knowledge, to deliver the present output.

[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] On 15/06/2018 the applicant informed EFSA that the petitioner changed from Eli Lilly and Company Ltd. to Elanco GmbH, Heinz-Lohmann-Str. 4. 27472 Cuxhaven, Germany.
[3] Commission Regulation (EC) No 1464/2004 of 17 August 2004 concerning the authorisation for 10 years of the additive 'Monteban' in feedingstuffs, belonging to the group of coccidiostats and other medicinal substances. OJ L 270, 18.8.2004, p. 8.
[4] Commission Regulation (EU) No 884/2010 of 7 October 2010 amending Regulation (EC) No 1464/2004 as regards the withdrawal time of the additive 'Monteban', belonging to the group of coccidiostats and other medicinal substances. OJ L 265, 8.10.2010, p. 4.
[5] FEED dossier reference: FAD-2015-0001.

EFSA has verified the EURL report as it relates to the methods used for the control of the active substance in animal feed/marker residue in tissues. The Executive Summary of the EURL report can be found in Annex A.[6]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of Monteban® G100 (narasin) for ducks is in line with the principles laid down in Regulation (EC) No 429/2008[7] and the relevant guidance documents: Guidance for the preparation of dossiers for coccidiostats and histomonostats (EFSA FEEDAP Panel, 2011a), Technical guidance: Tolerance and efficacy studies in target animals (EFSA FEEDAP Panel, 2011b), Technical Guidance for assessing the safety of feed additives for the environment (EFSA, 2008a), Guidance for establishing the safety of additives for the consumer (EFSA FEEDAP Panel, 2012a), Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012b) and Technical Guidance: Microbial Studies (EFSA, 2008b).

3. Assessment

The present opinion assesses the safety and efficacy of the coccidiostat Monteban® G100 containing narasin as active principle when used as a feed additive in ducks for fattening.

3.1. Characterisation

The additive Monteban® G100 is a feed additive authorised for the control of coccidiosis in chickens for fattening. It is intended to be used for the control of coccidiosis caused by *Tyzzeria perniciosa* and *Eimeria mulardi* in ducks.

The characterisation of the additive, the active substance and the producing strain, the manufacturing process and the technological properties of the additive have been recently reviewed in detail by the FEEDAP Panel (EFSA FEEDAP Panel, 2018).

The active ingredient is the polyether ionophore narasin which is produced by fermentation of a strain of *Streptomyces* spp. (NRRL 8092). Limited data on the taxonomic identification of the production strain were provided. Consequently, the identification of strain NRRL 8092 as *Streptomyces aureofaciens* is not demonstrated. The FEEDAP Panel cannot conclude on the absence of genetic determinants for antimicrobial resistance in *Streptomyces* spp. under assessment.

The final additive Monteban® G100 is produced by mixing narasin granulated with 10–25 g mineral oil, 10–20 g vermiculite (expanded vermiculite magnesium-aluminosilicate mineral) per kg additive and with rice hulls (the quantity is adjusted to ensure a narasin content of Monteban® G100 within the limit of specification). Monteban® G100 contains by specification 95.0–107.5 g narasin activity/kg.

The recommended inclusion level of Monteban® G100 in complete feed for ducks is 60–70 mg narasin/kg complete feed. Maximum residue limits (MRL) of 50 μg narasin/kg for all tissues and a withdrawal period of zero day is proposed.

3.2. Safety

3.2.1. Absorption, distribution, metabolism, excretion and residues

The metabolic fate of narasin in rat and chickens for fattening has been recently reviewed by the FEEDAP Panel (EFSA FEEDAP Panel, 2018). Considering that duck is physiologically similar to chicken, no specific studies need to be performed and the conclusions of the metabolism of narasin in chickens for fattening can be extrapolated to ducks: `(i) The main metabolic pathway of narasin in the chicken and rat involves oxidative processes leading to the formation of di-, tri- and tetra-hydroxynarasins as well as keto-narasins. (ii) Unchanged narasin is a minor component (up to 5%) of chicken excreta in the feed dose range proposed, whereas a great number of metabolites have been identified. Two major di-hydroxy and two major tri-hydroxy narasin metabolites represented together about 30% of the whole narasin related excreted compounds. (iii) Narasin metabolites in tissues and excreta are

[6] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/finirep-FAD-2015-0001-monteban.pdf

[7] 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.

qualitatively similar. The liver is the target tissue. A great number of narasin metabolites represent each less than 10% of the whole tissue residues. However, for control purposes skin/fat and narasin should be retained as practical target tissue and marker residue'.

The FEEDAP Panel noted that the proposed inclusion level in ducks is the same as the one in chickens for fattening (60–70 mg narasin/kg feed) and that the duration of administration is similar. In accordance with the FEEDAP Guidance on the Extrapolation of data from major species to minor species (EFSA, 2008c), no additional residue study is required in ducks and the assessment of consumer safety can be based on residue studies performed in chickens for fattening.

3.2.2. Safety for the target species

3.2.2.1. Tolerance in ducks for fattening

The tolerance study was made according to Good Clinical Practice, blinded and audited. A total of 360 one-day-old Pekin ducks of both sexes was allotted to five treatment groups which were fed diets containing Monteban® G100 at concentrations of 0, 70 (1x the maximum level), 140 (2x), 210 (3x) or 280 (4x) mg narasin/kg complete feed for at least 41 days.[8] The intended dietary narasin levels were analytically confirmed (within a margin of ± 20%). Group size was six replicates with six males and six female birds. Feed (starter for the first 2 weeks, followed by a grower diet) and water were provided for *ad libitum* intake. The analysis of the starter and grower feed showed values of 21.1% and 18.9% for crude protein, of 1.29% and 1.09% for lysine and of 0.35 and 0.32% for methionine, respectively. Body weight and feed consumption were determined weekly. At days 41, 42 or 43, four birds (two male and two female) per treatment were selected for blood sampling (haematology[9] and clinical chemistry[10]). On the same days, 12 birds (six male and six female, one from each pen) per treatment group were necropsied.

Statistical evaluation was done by analysis of variance (ANOVA). The pen was considered the statistical unit. Pairwise comparisons of the treated groups with control were conducted using Dunnett's test; differences were considered significant at a level of $p < 0.05$ (two-sided).

Ten birds died/were euthanised during the course of the study (seven of them in the control group).

At the end of the study (day 41), no significant differences between the groups were observed for body weight gain, feed consumption and feed to gain ratio. Mean values for females and males were 2,592 and 2,769 g for body weight gain, and 2.73 and 2.63 for feed to gain ratio, respectively.

The individual comparisons showed three significant differences to the control group: higher albumin and calcium concentrations of the use level group in males but not in females (not dose-related). For inorganic phosphate, there was a linear increase trend in females only, resulting in a significant difference of the 280 mg narasin/kg group (4x) from the control group. For males, a significant linear trend was found for leukocytes. Sodium was not analysed. In summary, there were no clinically relevant differences in the haematology and blood biochemistry between the control and the use level groups.

There was no difference in clinical observations. Necropsies did not reveal any difference in type and frequency of observed lesions between the treatment groups.

3.2.2.2. Interactions

Interactions between the ionophore narasin and other drugs have been recently reviewed by the FEEDAP Panel (EFSA FEEDAP Panel, 2018). The same conclusions can be applied to the use of Monteban® G100 in ducks, i.e. 'the simultaneous use of Monteban® G100 and certain antibiotic drugs (e.g. tiamulin) is contra-indicated'.

3.2.2.3. Microbial studies

The antimicrobial activity of narasin, as for other ionophoric compounds, is limited to Gram-positive bacteria. In a recent opinion on the same product (EFSA FEEDAP Panel, 2018), based on a literature review provided by the applicant, the Panel concluded that 'The use of narasin as feed additive is unlikely to induce resistance or cross-resistance to antimicrobials used in human and animal therapy.

[8] Technical dossier/Supplementray information June 2017/Annex 40.
[9] Red blood cell count, haemoglobin, mean corpuscular haemoglobin concentration, packed cell volume, white blood cell count, blood differential test, platelet comments and cellular morphology.
[10] Aspartate amino transferase, bile acid, protein (total), albumin, uric acid, creatine kinase, lactate dehydrogenase, phosphate, calcium, potassium, cholinesterase.

Narasin may increase *Salmonella*-shedding, but there is no reason to believe that narasin is different from other polyether ionophores in this respect'.

3.2.2.2. Conclusions on the safety for the target species

The highest applied use level 70 mg narasin from Monteban® G100/kg complete feed did not cause any adverse effects and is therefore considered safe for ducks for fattening with a margin of safety of about four.

The simultaneous use of Monteban® G100 and certain antibiotic drugs (e.g. tiamulin) is contraindicated.

Narasin is active against Gram-positive bacteria, while Gram-negative bacteria are resistant. The use of narasin as a feed additive is unlikely to induce resistance or cross-resistance to antimicrobials used in human and animal therapy. Narasin may increase *Salmonella*-shedding, but there is no reason to believe that narasin is different from other polyether ionophores in this respect. The simultaneous use of Monteban® G100 and certain antibiotic drugs (e.g. tiamulin) is contraindicated.

3.2.3. Safety for the consumer

3.2.3.1. Toxicological studies

In its recent opinion on the safety and efficacy of Monteban® G100 for chickens for fattening (EFSA FEEDAP Panel, 2018), the FEEDAP Panel re-assessed the toxicological studies available for narasin, submitted also in the current application, and concluded that: 'Narasin is not genotoxic. No indication of carcinogenicity or developmental toxicity was found at the doses tested in the mouse, rat and rabbit. The lowest no observed effect level (NOEL) identified in the oral toxicity studies was 0.5 mg/kg bw per day for the neuropathy seen in a one-year dog study. Since this dose is above the lowest NOAEL previously identified of 0.5 mg/kg bw per day, there is no reason to consider acute cardiovascular effects in the risk assessment. The no observed adverse effect level (NOAEL) of 0.5 mg/kg bw per day is an appropriate base for confirming the acceptable daily intake (ADI) of 0.005 mg narasin/kg bw already established by the FEEDAP Panel in its former opinions applying a uncertainty factor of 100'.

3.2.3.2. Assessment of consumer safety

The FEEDAP Panel already assessed the safety of the consumer exposed to narasin residues from chicken tissues and concluded that the use of Monteban® G100 in chickens for fattening at the maximum dose proposed, and without applying a withdrawal period, is safe for the consumer (EFSA FEEDAP Panel, 2010, 2018). Exposure of adults to total narasin residues from edible chicken tissues would not exceed 20% of the ADI based on the conventional food basket of Regulation (EC) no 429/2008. Maximum residue limits (MRL) of 50 μg narasin/kg for all wet tissues ensure consumer safety, MRL-derived residues would account for 58% of the ADI. Applying European food consumption data from EFSA's Comprehensive European Food Consumption Database (see Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017)), both values would decrease to 2% and 20%, respectively. All exposure levels indicate a large margin of safety for adults consuming chicken tissues.

Since metabolic proximity between the major species chicken and the minor species duck is considered to be given, no additional residue studies are required for a minor species when the application level and duration are similar. Assuming that the residues in duck tissues would be of the same magnitude as those measured in the physiologically similar major species (see Section 3.2.2.1), the above conclusions apply to the use of Monteban® G100 in the duck. This includes that no withdrawal time is necessary and that the MRLs established from studies with chickens is taken for ducks. Considering the large margin of safety established for adults consuming tissues from treated chicken, the extrapolations made from chicken to duck have a very low level of uncertainties.

3.2.3.3. Conclusion on safety for the consumer

The FEEDAP Panel concludes that the use of Monteban® G100 at a maximum concentration of 70 mg/kg complete feed for ducks for fattening is safe for the consumer. A withdrawal period is not necessary and the same MRL of 50 μg narasin/kg for all wet tissues as established for chickens applies to duck tissues.

3.2.4. Safety for the user

As the product is identical to the one recently re-evaluated by the FEEDAP Panel (EFSA FEEDAP Panel, 2018), the same conclusions can be reiterated: 'Monteban® G100 is irritant to the eyes but not to the skin. It has the potential to induce skin sensitisation. The acute systemic toxicity following dermal application is low. Inhalation exposure would pose a risk to persons handling the additive'.

3.2.5. Safety for the environment

In accordance with the Technical guidance on the extrapolation from major species to minor species regarding the assessment of feed additives for use in animal nutrition (EFSA, 2008c), the environmental risk assessment for ducks can be extrapolated from the assessment done for the use of narasin in the major species. Recently (EFSA FEEDAP Panel, 2018), the FEEDAP Panel concluded that: 'Narasin, when used as feed additive for chickens for fattening at 70 mg/kg feed, is not expected to pose a risk to the environment. The risk for sediment compartment cannot be assessed. Narasin is not considered to have a bioaccumulation potential'.

As the conditions of use among poultry species are similar, the same conclusion applies to the use of the additive in ducks.[11]

3.3. Efficacy

The applicant submitted one floor pen study in ducks and three floor pen studies and three anticoccidial sensitivity tests (AST) in chickens for fattening.

3.3.1. Floor pen study in ducks

For a coccidiostat already approved in a major species, only one study in a minor species is necessary to conclude on efficacy.

The floor pen study in ducks for fattening was performed in 2014.[12] Ninety-six 1-day-old Peking ducks were randomly allocated to an uninfected untreated control (UUC) group, an infected untreated control (IUC) group and an infected treated (IT) group receiving 60 mg narasin/kg feed (analysed 44.8–66.6 mg narasin/kg feed). Group size was four pens with eight animals per pen. The duration of the trial was 56 days. On day 14, all birds in the IUC and IT groups were inoculated by individual oral gavage with 61,372 oocysts of a recent field isolate of duck coccidia. This inoculum containing *Eimeria anatis*, *Tyzzeria perniocosa* and *Wenyonella* spp. had been shown in a pilot virulence test to yield mild to moderate signs of coccidiosis following artificial challenge with approximately 75,000 sporulated oocysts. Body weight and feed consumption were measured for the first 4 week at weekly intervals followed by biweekly measurements until the end of the study. Feed to gain ratios were calculated for the corresponding intervals. Statistical analysis of the zootechnical data was done by comparing the infected groups with UUC and the treated groups (IT) with the IUC by parametric testing (in case assumptions are fulfilled, method not mentioned) or non-parametric testing (Wilcoxon Mann-Whitney U test). The statistical tests were two-sided with a 5% significance level.

There was no coccidiosis-related mortality in the study. All the bird losses from day 1 to 28 were related to adenovirus.[13] In the period of days 15–28, a total of 14 ducks were found dead or were euthanised because of illness (in the UUC, IUC and IT groups, 3, 8 and 3 ducks, respectively). Total losses were three in the UUC group, nine in the IUC group and four in the IT group. Any statistical outcome of mortality testing is not relevant since only coccidiosis mortality would count for efficacy.

Oocyst excretion and faecal litter scores were measured and clinical observations were recorded. For these endpoints, which are relevant in the assessment of coccidiostatic activity, no statistical analysis was provided.

[11] The FEEDAP Panel is aware of the fact that under certain husbandry conditions of ducks (i.e. lakes, ponds and rivers), narasin and its metabolites from droppings can be directly released to surface water.
[12] Technical dossier/Section IV/Annex 14.
[13] To aid a potential effect of *Eimeria* inoculation, an immunosuppressant substance (betamethasone) was administered via water for drinking to all birds from days 13–17. This may have also promoted the severity of an adenovirus infection.

Mean faecal oocyst counts in the IT narasin group (OPG: 625) were lower compared to the IUC group (OPG: 30,438) on day 19. In the UUC, no oocyst were found throughout the study. On day 35, no oocysts were found in all groups.

The faecal litter score value[14] in the IT narasin group (1.75/1.0/1.0) was lower than in the IUC group (2.5/2.0/1.25) on days 20, 21 and 22. The faecal litter score value in the UUC group was 1.0 throughout the days of assessment.

The daily weight gain in the week (days 13–21) after artificial infection was 29.2 g/duck in the UUC group, 22.9 g in the IUC (significant depression), 28.6 g in the IT group. The final body weight was not significantly different between groups (UUC 4,020 g, IUC 3,920 g, IT 4,060 g). The feed to gain ratio was not significantly different between IT (4.98) and IUC group (5.42) in the critical period days 13–21 and over the total period days 1–56 (2.61; 2.85). The feed to gain ratio of the UUC group was 4.57 for the period days 13–21 and 2.68 for days 1–56.

Faecal oocyst counts and faecal litter scores indicate the effect of inoculation resulting in clinical coccidiosis. The infection was weak, clinical signs disappeared a few weeks after infection. Oocyst excretion was clearly suppressed by narasin as faecal score was improved compared to the infected untreated control, however, not statistically analysed. These effects are in line with the better, although not significant ($p < 0.08$), body weight gain of the treated ducks in the period immediately after inoculation.

The study shows several weaknesses in conduct and reporting: (i) the inoculum was of low pathogenicity so that an immunosuppressive drug (betamethasone) had to be administered via water for drinking for 4 days after infection, (ii) the relevant endpoints (oocyst excretion and faecal litter scores) were not statistically evaluated, and (iii) the statistical output is mainly limited to tables without any text explanation.

Based on the data above, Monteban® G100 has not been proven to be efficacious in controlling coccidiosis in ducks.

3.3.2. Floor pen study in chickens for fattening

The studies in chickens for fattening were described and assessed in a recent opinion of the FEEDAP Panel (EFSA FEEDAP Panel, 2018). It was concluded that 'The efficacy of Monteban® G100 was demonstrated in three floor pen studies and in two ASTs, a third AST lacking to show anticoccidial efficacy. The FEEDAP Panel is therefore not in a position to conclude on the efficacy of Monteban® G100 at the minimum applied dose of 60 mg narasin/kg complete feed for chickens for fattening'.

3.3.3. Conclusions on efficacy

The FEEDAP Panel is not in the position to conclude on the efficacy of Monteban® G100 in controlling coccidiosis in ducks for fattening because the efficacy was not demonstrated neither in the major species (chickens for fattening) nor in the minor species (ducks).

3.3.4. Post-market monitoring

Field monitoring of *Eimeria* spp. resistance to narasin should be undertaken, preferably during the latter part of the period of authorisation.

4. Conclusions

Narasin from Monteban® G100 is safe for ducks for fattening at a level of 70 mg/kg complete feed with a margin of safety of about four. The simultaneous use of Monteban® G100 and certain antibiotic drugs (e.g. tiamulin) is contraindicated.

The ADME of narasin is considered to be similar in the duck and chicken, two physiologically similar species. The FEEDAP Panel assumes that the residues in duck tissues would be of the same magnitude as those measured in chicken tissues. The FEEDAP Panel concludes that the use of Monteban® G100 at a maximum concentration of 70 mg/kg complete feed for ducks for fattening is safe for the consumer. For ducks a withdrawal period is not necessary and the same MRL of 50 μg narasin/kg for all wet tissues as established for chickens applies to duck tissues.

[14] Faecal aspect within each pen was assessed and given a score based on consistency as follows: Score 1 = Normal; Score 2 = Any in pen showing mucous consistency, faeces still well formed; Score 3 = All showing mucous consistency, some well formed, some runny; Score 4 = All showing runny mucous consistency.

Monteban® G100 is irritant to the eyes but not to the skin. It has the potential to induce skin sensitisation. The acute systemic toxicity following dermal application is low. Inhalation exposure would pose a risk to persons handling the additive.

Narasin, when used as a feed additive for ducks for fattening at 70 mg/kg feed, is not expected to pose a risk to the environment. The risk for sediment compartment cannot be assessed. Narasin is not considered to have a bioaccumulation potential.

Insufficient data were provided to allow a conclusion on the efficacy of Monteban® G100 in ducks.

5. Recommendations

Narasin is toxic to horses, turkeys and rabbits at levels below those used in the prevention of coccidiosis in chickens.

Documentation provided to EFSA

1) Monteban® G100 for ducks. January 2015. Submitted by Eli Lilly and Company Ltd.
2) Monteban® G100 for ducks. Supplementary information. October 2015. Submitted by Eli Lilly and Company Ltd. (not complete)
3) Monteban® G100 for ducks. Supplementary information. June 2017. Submitted by Eli Lilly and Company Ltd.
4) Evaluation report of the European Union Reference Laboratory for Feed Additives on the Methods of Analysis for Monteban® G100.
5) Comments from Member States.

Chronology

Date	Event
7/1/2015	Dossier received by EFSA
13/1/2015	Reception mandate from the European Commission
28/4/2015	Application validated by EFSA – Start of the scientific assessment
8/6/2015	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: Evaluation method*
25/6/2015	Request of additional supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003. *Issues: Characterisation*
17/5/2014	Comments received from Member States
27/10/2015	Reception of supplementary information from the applicant - The information was considered not complete. Applicant was informed via email dated 30/11/2015. The scientific assessment remained suspended
17/5/2016	Request of additional supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003. *Issues: Safety for the target species, Safety for the environment*
19/1/2016	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives
28/6/2017	Reception of supplementary information from the applicant - Scientific assessment re-started
3/10/2018	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

References

EFSA (European Food Safety Authority), 2004. Opinion of the Scientific Panel on Additives and Products or Substances used in Animal Feed on the re-evaluation of efficacy and safety of the coccidiostat Monteban® G100 in accordance with article 9G of Council Directive 70/524/EEC. EFSA Journal 2004;90, 1–44. Available online: http://www.efsa.europa.eu/en/efsajournal/doc/90.pdf

EFSA (European Food Safety Authority), 2008a. Technical Guidance of the Scientific Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) for assessing the safety of feed additives for the environment. EFSA Journal 2008;6(10):842, 28 pp. https://doi.org/10.2903/j.efsa.2008.842

EFSA (European Food Safety Authority), 2008b. Technical Guidance: microbial Studies. EFSA Journal 2008;6 (10):836, 3 pp. https://doi.org/10.2903/j.efsa.2008.836

EFSA (European Food Safety Authority), 2008c. Technical Guidance: Extrapolation of data from major species to minor species regarding the assessment of additives for use in animal nutrition. EFSA Journal 2008;6(9):803, 5 pp. https://doi.org/10.2903/j.efsa.2008.803

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2010. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP); Scientific Opinion on the modification of authorisation of the feed additive Monteban® G100 (narasin) for chickens for fattening on request from European Commission. EFSA Journal 2010;8(3):1549, 10 pp. https://doi.org/10.2903/j.efsa.2010.1549. Available online: www.efsa.europa.eu

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2011a. Guidance for the preparation of dossiers for coccidiostats and histomonostats. EFSA Journal 2011;9(5):2174, 12 pp. https://doi.org/10.2903/j.efsa.2011.2174

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2011b. Technical guidance: tolerance and efficacy studies in target animals. EFSA Journal 2011;9(5):2175, 15 pp. https://doi.org/10.2903/j.efsa.2011.2175

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012a. Guidance for establishing the safety of additives for the consumer. EFSA Journal 2012;10(1):2537, 12 pp. https://doi.org/10.2903/j.efsa.2012.2537

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012b. Guidance on studies concerning the safety of use of the additive for users/workers. EFSA Journal 2012;10(1):2539, 5 pp. https://doi.org/10.2903/j.efsa.2012.2539

EFSA FEEDAP Panel (EFSA Panel on Products or Substances used in Animal Feed), 2017. Guidance on the assessment of the safety of feed additives for the consumer. EFSA Journal 2017;15(10):5022, 17 pp. https://doi.org/10.2903/j.efsa.2017.5022

EFSA Feedap Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis V, Azimonti G, Bastos ML, Christensen H, Dusemund B, Kouba M, Kos Durjava M, Lopez-Alonso M, Lopez Puente S, Marcon F, Mayo B, Pechova A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen R, Aquilina G, Bories G, Brantom P, Cocconcelli PS, Halle I, Kolar B, Wester P, van Beelen P, Holczknecht O, Vettori MV and Gropp J, 2018. Scientific Opinion on the safety and efficacy of Monteban® G100 (narasin) for chickens for fattening. EFSA Journal 2018;16(11):5460, 38 pp. https://doi.org/10.2903/j.efsa.2018.5460

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2012. Evaluation of certain veterinary drug residues in food: seventy-fifth report of the Joint FAO/WHO Expert Committee on Food Additives. (WHO technical report series; no. 969).

Abbreviations

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and excretion
AST	anticoccidial sensitivity tests
bw	body weight
EURL	European Union Reference Laboratory
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
LOQ	limit of quantification
MRL	maximum residue limit
NOAEL	no observed adverse effect level
NOEL	no observed effect level

Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Methods of Analysis for Monteban® G100

Monteban® G100 is a feed additive currently authorised for *chickens for fattening* by Commission Regulation (EC) No 1464/2004 belonging to the group 'Coccidiostats and other medicinal substances' listed in Chapter I of Annex B of Directive 70/524/EEC. In the current application authorisation under article 4 (1) of the Regulation (EC) No 1831/2003 is sought for *ducks*. *Monteban® G100* consists of 10% (w/w) of *narasin* (active substance), rice hulls, mineral oil and verxite. The Applicant suggested a concentration of *narasin* in *feedingstuffs* ranging from 60 to 70 mg/kg. Furthermore, the Applicant suggests maximum residue limits (MRLs) 50 μg/kg for all relevant duck *tissues*.

For the quantification of *narasin* in the *feed additive*, *premixtures* and *feedingstuffs*, the Applicant submitted two single-laboratory validated and further verified methods based on EN ISO 14183 using high-performance liquid chromatography with post-column derivatisation coupled to spectrophotometric detection (HPLC-PCD-UV-Vis). Based on the performance characteristics provided, the EURL recommends for official control the HPLC-PCD-UV-Vis method for the quantification of *narasin* in the *feed additive* and the EN ISO 14183 for the quantification of *narasin* in *feedingstuffs*.

For the quantification of *narasin* in *tissues*, the Applicant submitted a single laboratory validated (in chicken *tissues*) and further verified (in a duck *tissue*) method based on RP-HPLC coupled to a triple quadrupole mass spectrometer (MS/MS) in electrospray ionisation (ESI) mode using matrix matched standards, similar to the one developed and validated by the European Union Reference Laboratory for Pharmacologically Active Substances (BVL). The satisfactory performance characteristics provided by the Applicant for the tissues of concern demonstrate that (i) the method proposed by the Applicant is equivalent to the BVL method, (ii) the Applicant method is also applicable to kidney and skin/fat tissues and (iii) the Applicant method is also applicable to duck *tissues*. Based on the performance characteristics presented, the EURL recommends for official control the single laboratory validated and further verified RP-HPLC–MS/MS method proposed by the Applicant to enforce the *narasin* MRLs in the relevant *tissues*.

Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by Article 10 (Commission Regulation (EC) No 378/2005) is not considered necessary.