Efficacy of a feed additive consisting of nicarbazin (Coxar®) for use in turkeys for fattening (Huvepharma N.V.)

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, Mojca Fašmon Durjava, Maryline Kouba, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa, Ruud Woutersen, Jürgen Gropp, Guido Rychen, Orsolya Holczknecht and Maria Vittoria Vettori

Abstract

Following a request from the European Commission, the Panel on Additives and Products or substances used in Animal Feed (FEEDAP Panel) was asked to deliver a scientific opinion on the efficacy of the coccidiostat nicarbazin (Coxar®) when used in feed for turkeys for fattening. On the basis of the new data provided, the FEEDAP Panel updated its previous conclusions on the efficacy of Coxar® as follows: the two new floor pen studies showed efficacy of nicarbazin from Coxar® reducing the adverse clinical consequences of an Eimeria infection in turkeys. Overall, when considering also the positive floor pen study previously reported and the three positive anticoccidial sensitivity tests, the FEEDAP Panel concludes that Coxar® has the potential to be efficacious against coccidiosis of turkeys for fattening at 100 mg nicarbazin/kg complete feed.

© 2022 Wiley-VCH Verlag GmbH & Co. KgaA on behalf of the European Food Safety Authority.

Keywords: Coxar®, nicarbazin, coccidiostats, turkeys for fattening, efficacy

Requestor: European Commission
Question number: EFSA-Q-2021-00104
Correspondence: feedap@efsafea.europa.eu
Panel members: Giovanna Azimonti, Vasileios Bampidis Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Mojca Fasmon Durjava, Maryline Kouba, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa and Ruud Woutersen.

Declarations of interest: The declarations of interest of all scientific experts active in EFSA’s work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch.

Acknowledgements: The Panel wishes to acknowledge the contribution of Montserrat Anguita and Jordi Tarrés-Call to this opinion.

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, Fasmon Durjava M, Kouba M, López-Alonso M, López Puente S, Marcon F, Mayo B, Pechová A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen R, Gropp J, Rychen G, Holczknecht O and Vettori MV, 2022. Scientific Opinion on the efficacy of a feed additive consisting of nicarbazin (Coxar®) for use in turkeys for fattening (Huvepharma N.V.). EFSA Journal 2022;20(2):7162, 7 pp. https://doi.org/10.2903/j.efsa.2022.7162

ISSN: 1831-4732
© 2022 Wiley-VCH Verlag GmbH & Co. KgaA on behalf of the European Food Safety Authority.

This is an open access article under the terms of the Creative Commons Attribution-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited and no modifications or adaptations are made.

The EFSA Journal is a publication of the European Food Safety Authority, a European agency funded by the European Union.
Table of contents

Abstract .................................................................................................................................................... 1
1. Introduction ........................................................................................................................................ 4
   1.1. Background and Terms of Reference as provided by the requestor .................................................. 4
2. Data and methodologies ...................................................................................................................... 4
   2.1. Data ................................................................................................................................................... 4
   2.2. Methodologies ..................................................................................................................................... 4
3. Assessment ......................................................................................................................................... 4
   3.1. Efficacy .............................................................................................................................................. 5
4. Conclusions ......................................................................................................................................... 7
5. Documentation as provided to EFSA/Chronology .................................................................................... 7
References ................................................................................................................................................ 7
Abbreviations ............................................................................................................................................ 7
1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1831/2003 establishes the rules governing the Community authorisation of additives for use in animal nutrition and, in particular Article 9 defines the terms of the authorisation by the Commission.

The applicant, Huvepharma NV, is seeking a Community authorisation of Nicarbazin as a feed additive to be used as a coccidiostat and histomonostats for turkeys for fattening (Table 1).

Table 1: Description of the substances

| Category of additive | Functional group of additive | Description | Target animal category | Applicant | Type of request |
|----------------------|-----------------------------|-------------|------------------------|-----------|-----------------|
| Coccidiostats and histomonostats | Coccidiostat | Nicarbazin | Turkeys for fattening | Huvepharma NV | New opinion |

On 6 March 2018, the Panel on Additives and Products or Substances used in Animal Feed of the European Food Safety Authority ("Authority"), in its opinion on the safety and efficacy of the product, could not conclude on the efficacy of Nicarbazin.

After the discussion with the Member States at a meeting of the Standing Committee on Plants, Animals, Food and Feed (Animal Nutrition section), it was suggested to check for the possibility to demonstrate the efficacy of the additive.

The Commission gave the possibility to the applicant to submit complementary information and data in order to complete the assessment and to allow a revision of Authority's opinion. The new data has been received on 26 January 2021 and were already transmitted to the Authority by the applicant.

In view of the above, the Commission asks the Authority to deliver a new opinion on the efficacy of Nicarbazin as a feed additive for turkeys for fattening based on the additional data submitted by the applicant, in accordance with Article 29(1)(a) of Regulation (EC) No 178/2002.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of additional information to a previous application of the same product.

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety for the environment and the efficacy of Coxar® (nicarbazin) is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance document: Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018a).

3. Assessment

Coxar®, containing nicarbazin as the active substance, is a feed additive intended to be used for the prevention of coccidiosis in turkeys for fattening up to 16 weeks of age at a dose of 100 mg nicarbazin/kg complete feed.

In 2018, the FEEDAP Panel adopted an opinion on the safety and efficacy of Coxar® (nicarbazin) for turkeys for fattening (EFSA FEEDAP Panel, 2018b) and concluded that the additive is safe for the target species, consumers and users. No conclusions on the safety for the environment and efficacy

---

1 FEED dossier reference: FAD-2021-0005.
2 FEED dossier reference: FAD-2015-0039.
3 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.
could be made. In 2021, based on additional data submitted by the applicant, the FEEDAP Panel updated its former assessment and concluded that the use of nicarbazin from Coxar® in complete feed for turkeys does not pose a risk for the environment (EFSA FEEDAP Panel, 2021).

In the present opinion, the efficacy of Coxar® is assessed based on additional data submitted by the applicant.

3.1. Efficacy

In the former opinion (EFSA FEEDAP Panel, 2018b), the anticoccidial efficacy of nicarbazin from Coxar® was demonstrated in three anticoccidial sensitivity tests (AST), but only in one floor pen study. In the current assessment, the applicant submitted two new floor pen studies conducted in 2020 (Table 2).

In trial 1, one-day-old male turkeys (Hybrid Converter) were penned and distributed into three experimental groups: an uninfected untreated control group (UUC), an infected untreated control group (IUC) and an infected treated group (IT). The birds received diet based on maize, wheat and soybean meal in pellet form and on ad libitum basis for a total of 85 days. The IT group’s diet contained 100 mg nicarbazin/kg feed and the intended dietary concentration was analytically confirmed (Table 2). In the infected groups (IUC and IT), all birds were inoculated orally via a syringe with recent field isolates of pathogenic *Eimeria* species. Animal health and mortality were monitored daily. Feed intake and body weight of the animals were measured, feed to gain ratio was calculated. Samples of excreta were analysed for oocyst excretion at days 20, 21, 22, 29, 36 and 85. Intestinal lesions were scored on five birds per pen, according to the method of El-Sherry et al. (2018) and Gadde et al. (2020), with a score from 0 (no lesions) to 4 (severe lesions) at days 20, 21, 29 and 85. In addition, faecal scoring was done (score 0: normal droppings; score 1: diarrhoea) on days 20, 21, 29 and 36.

The lesions scores, oocysts excretion, clinical behaviour and zootechnical parameters data were analysed with a general linear mixed model with treatment as fixed effect. The pen was the experimental unit for statistical purposes. For overall mortality and coccidiosis-related mortalities, a Cox proportional hazard model was fit to analyse the differences in mortality between the groups. All hypothesis tests were conducted at the 0.05 level of significance.

Trial 2 followed a similar design. One-day-old male turkeys (Wirral White) were penned and distributed into three experimental groups: UUC, IUC and IT. The birds received diet based on barley, wheat and soya in crumb (for starter diet) or pellet (for grower diet) forms and on ad libitum basis for a total of 84 days. The IT group diet contained 100 mg nicarbazin/kg feed and the intended dietary concentration was analytically confirmed (Table 2). In the infected groups, all birds were inoculated orally via a syringe with a single dose of ~15,000 oocysts/bird. Animal health and mortality were monitored daily. Feed intake and body weight of the animals were measured, feed to gain ratio was calculated. On days 27, 35 and 84, two birds from each pen were killed for intestinal lesion scoring. The scoring was based on an in-house scoring system with scores from 0 (no lesions) to 4 (severe lesions). Samples of excreta were analysed for oocyst excretion on days 21, 26–30, 35, 42, 63 and 84.

The data was analysed with parametric or non-parametric tests and group means were compared with Dunnett’s test.

---

4 Study report P20214-FP and its amendments submitted in July 2021 and December 2021.
5 The inocula used in trial 1 was tested for its virulence in a dose-titration study. At day 5 post inoculation (PI), the doses selected (see Table 2) resulted in lesion scores of 2.0 (intestinal) and 1.5 (caecal) and a weight gain reduction of 20%. At day 6 PI, the lesions scores were 4.0 (both intestinal and caecal) and mortality was 80%.
6 Study report RRTU-232-20-06 and its amendments submitted in July 2021 and December 2021.
7 The inocula used in trial 2 was tested for its virulence in a dose-titration study. At day 6 PI, the doses selected (see Table 2) resulted in lesion scores of 2.6 (*E. adenoeides/meleagridis*), 1.2 (*E. gallopavonis*) and 1.4 (*E. meleagrimitis*) and a weight gain reduction of 30%.
The results on the mortality are shown in Table 3. In trial 1, coccidiosis-related mortality was significantly reduced in the IT group (8.5%) when compared to the IUC group (25.4%) in the period between 5 and 8 days post-inoculation (PI). No mortality was observed afterwards. In trial 2, there was no coccidiosis related mortality in any of the treatment groups after inoculation.

With regard intestinal lesions scores (ILS), overall, no significant effect of the additive was observed on ILS in trial 1; however, when the analysis included also the birds dying of coccidiosis, ILS on day 6 PI for *Eimeria adenoeides/Eimeria gallopavonis* was significantly lower in IT (2.7) than in IUC (3.0). In trial 2, mean total ILS on day 6 PI were low (1.71, 3.38 and 2.25 for UUC, IUC and IT, respectively) which is in line with the lack of mortality in this trial. The highest difference between IT and IUC was noted in case of *E. gallopavonis* (0.54 and 1.29, \( p = 0.007 \)). In line with these results, the percent of birds with ILS above 2 for lesions due to *E. gallopavonis* in the IT group was significantly lower than in the IUC group (4% against 38%, \( p = 0.01 \)).

In both trials, no significant effect of Coxar® was noted on the reduction of oocysts excretion whatever the time point. In trial 1, no changes in faecal consistency were observed in any of the groups on any of the scoring days.

Table 3 shows the cumulative results of the performance parameters. In trial 1, body weight was significantly higher in the IT group compared to IUC at 6 days PI (538 g vs. 478 g) and at the end of the study. In trial 2, feed intake in the IT group was significantly higher than in the IUC at the end of the trial. Daily weight gain was significantly better in the IT group than in the IUC only in the periods 6–14, 14–21 and 21–28 days PI (39 vs. 31 g; 50 vs. 40 g and 71 vs. 65 g) but not at study end.

The results on mortality are shown in Table 3. In trial 1, coccidiosis-related mortality was significantly reduced in the IT group (8.5%) when compared to the IUC group (25.4%) in the period between 5 and 8 days post-inoculation (PI). No mortality was observed afterwards. In trial 2, there was no coccidiosis related mortality in any of the treatment groups after inoculation.

With regard intestinal lesions scores (ILS), overall, no significant effect of the additive was observed on ILS in trial 1; however, when the analysis included also the birds dying of coccidiosis, ILS on day 6 PI for *Eimeria adenoeides/Eimeria gallopavonis* was significantly lower in IT (2.7) than in IUC (3.0). In trial 2, mean total ILS on day 6 PI were low (1.71, 3.38 and 2.25 for UUC, IUC and IT, respectively) which is in line with the lack of mortality in this trial. The highest difference between IT and IUC was noted in case of *E. gallopavonis* (0.54 and 1.29, \( p = 0.007 \)). In line with these results, the percent of birds with ILS above 2 for lesions due to *E. gallopavonis* in the IT group was significantly lower than in the IUC group (4% against 38%, \( p = 0.01 \)).

In both trials, no significant effect of Coxar® was noted on the reduction of oocysts excretion whatever the time point. In trial 1, no changes in faecal consistency were observed in any of the groups on any of the scoring days.

Table 3 shows the cumulative results of the performance parameters. In trial 1, body weight was significantly higher in the IT group compared to IUC at 6 days PI (538 g vs. 478 g) and at the end of the study. In trial 2, feed intake in the IT group was significantly higher than in the IUC at the end of the trial. Daily weight gain was significantly better in the IT group than in the IUC only in the periods 6–14, 14–21 and 21–28 days PI (39 vs. 31 g; 50 vs. 40 g and 71 vs. 65 g) but not at study end.

In summary, Coxar® significantly reduced coccidiosis related mortality in one trial, while in a second trial the challenge with *Eimeria* inoculation did not provoke any mortality. In both studies, intestinal lesions due to *E. adenoeides/E. gallopavonis* or *E. gallopavonis* were lower in the treated group.
compared to the IUC at 6 days post inoculation. Coxar® did not influence oocyst excretion of turkeys. Some of the secondary endpoints (body weight gain and feed intake) were improved in the IT group compared to IUC at the end of the study and/or shortly after the inoculation.

4. Conclusions

The two new floor pen studies showed efficacy of nicarbazin from Coxar® reducing the adverse clinical consequences of an Eimeria infection in turkeys.

Overall, when considering also the positive floor pen study previously reported and the three positive AST, the FEEDAP Panel concludes that Coxar® has the potential to be efficacious against coccidiosis of turkeys for fattening at 100 mg nicarbazin/kg complete feed.

5. Documentation as provided to EFSA/Chronology

| Date       | Event                                                                 |
|------------|-----------------------------------------------------------------------|
| 04/01/2021 | Dossier received by EFSA. Additional data on Coxar® (nicarbazin) for turkeys for fattening regarding the efficacy submitted by Huvepharma N.V. |
| 03/02/2021 | Reception mandate from the European Commission                         |
| 02/03/2021 | Acceptance of the mandate by EFSA – Start of the scientific assessment |
| 28/05/2021 | Request for clarification to the applicant Article 7(3) of Commission Regulation (EC) No 1304/2003 – Scientific assessment suspended. |
| 23/07/2021 | Reception of supplementary information from the applicant - Scientific assessment re-started |
| 19/10/2021 | Request for clarification to the applicant Article 7(3) of Commission Regulation (EC) No 1304/2003 – Scientific assessment suspended. |
| 01/12/2021 | Reception of supplementary information from the applicant - Scientific assessment re-started |
| 27/01/2022 | Opinion adopted by the FEEDAP Panel. End of the Scientific assessment  |

References

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Galobart J, Innocenti ML and Martino L, 2018a. Guidance on the assessment of the efficacy of feed additives. EFSA Journal 2018;16(5):5274, 25 pp. https://doi.org/10.2903/j.efsa.2018.5274

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Brantom P, Halle I, van Beelen P, Holczknecht O, Vettori MV and Gropp J, 2018b. Scientific Opinion on the safety and efficacy of Coxar® (nicarbazin) for turkeys for fattening. EFSA Journal, 2018;16(4):5214, 18 pp. https://doi.org/10.2903/j.efsa.2018.5214

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis V, Bastos ML, Christensen H, Dusemund B, Fasmon Durjava M, Kouba M, López-Alonso M, López Puente S, Marcon F, Mayo B, Pechevá A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen R, Finizio A, Focks A, Teodorovic I, Vettori MV and Azimonti G, 2021. Scientific Opinion on the safety for the environment of a feed additive consisting of nicarbazin (Coxar®) for use in turkeys for fattening (Huvepharma N.V.). EFSA Journal 2021;19(7):6715, 11 pp. https://doi.org/10.2903/j.efsa.2021.6715

El-Sherry S, Ogedengbe ME, Hafeez MA, Sayf-Al-Din M, Gad N and Barta JR, 2018. Cecal coccidiosis in turkeys: Comparative biology of Eimeria species in the lower intestinal tract of turkeys using genetically typed, single oocyst-derived lines. Protozoology, 28, 30–36.

Gadde UD, Rathinam T, Finklin MN and Chapman HD, 2020. Pathology caused by three species of Eimeria that infect the turkey with a description of a scoring system for intestinal lesions. Avian Pathology, 49, 80–86.

Abbreviations

AST anticoccidial sensitivity tests
FEEDAP EFSA Panel on Additives and Products or Substances used in Animal Feed
UUC uninfected untreated control
IUC infected untreated control
IT infected treated