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

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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.

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

Requestor: European Commission

Question number: EFSA-Q-2021-00104

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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	Coccidiostats and histomonostats
Functional group of additive	Coccidiostat
Description	Nicarbazin
Target animal category	Turkeys for fattening
Applicant	Huvepharma NV
Type of request	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[1] to a previous application of the same product.[2]

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[3] 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,[4] 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.[5] 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[6] 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.[7] 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%.

Table 2: Experimental design of floor pen studies with turkeys for fattening using Coxar®

Trial no (Date of conduct)	Replicates per treatment (Birds per replicate)	Inoculum characteristics				Feed analysis in the diets(2) nicarbazin (mg/kg feed)
		Country, date of isolation	Intended dose (number of oocysts) and strain per bird		Day of inoculation	
1 (8/2020)	8 (22)	Poland 5/2019	*E. meleagrimitis/ E. adenoeides*	199,000	Day 15	Starter: 96 Grower: 98
			E. meleagridis/ E. gallopavonis	43,000		
2 (9/2020)	12 (8)	UK 06/2020	Total oocyst(1)	15,000	Day 21	Starter: 109 Grower: 106

(1): Inoculum contained the following species: *E. adenoeides*, *E. gallopavonis*, *E. meleagridis*, *E. meleagrimitis*.
(2): In trial 1, birds received starter diet from day 0 until 14 (26.9% crude protein (CP), 11.9 MJ metabolisable energy (ME)/kg), grower diet from day 14 until 50 (23.9% CP, 12.4 MJ ME/kg) and finisher diet (20.2% CP, 12.3 MJ ME/kg) from day 50 until study end. In trial 2, birds received starter diet from day 0 until 35 (28.0% CP, 12.4 MJ ME/kg) and grower diet from day 35 until study end (24.5% CP, 12.6 MJ ME/kg).

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 *Eimera 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.

Table 3: Cumulative zootechnical parameters and mortality of turkeys fed Coxar®

	Feed intake (g/day)	Body weight(1) (kg)	Weight gain (g/day)	Feed to gain ratio	Mortality % (n)
Trial 1					
UUC	147	6.71*	78	1.71	0*
IUC	141	5.98	70	1.95	25.4 (44)
IT	141	6.34*	74	1.81	8.5* (15)
Trial 2					
UUC	158	6.60	79	2.01	0
IUC	150	6.42	76	2.00	0
IT	159*	6.56	78	2.04	0

*: IT or UUC means significantly different from IUC mean ($p \leq 0.05$).
(1): In trial 2, the total weight gain is indicated instead of final body weight.

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

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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