Assessment of the consumer safety of amprolium hydrochloride (Coxam®) as a feed additive for all chickens for fattening and reared for laying

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Regulated Products Risk Assessment Unit
Science, Evidence and Research Division, FSA

Risk Assessment Team
Science Division, FSS

Regulated Product Dossier Assessment
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Abbreviations

Acronym	Definition
ACAF	Advisory Committee on Animal Feedingstuffs
AFFAJEG	Animal Feed and Feed Additives Joint Expert Group
ADI	Acceptable daily intake
CAS	Chemical Abstracts Service
CVMP	Committee for Medicinal Products for Veterinary Use – Currently the Committee for Medicinal Products for Veterinary Use
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
EURL	European Union Reference Laboratory
FSA	Food Standards Agency
FSS	Food Standards Scotland
IE-HPLC-UV	Cation Exchange High Performance Liquid Chromatography coupled to Ultraviolet detection
LOQ	Limit of quantification
MRLs	Maximum residue limits
NOAEL	No observed adverse effect level
NP-HPLC	Normal Phase High-Performance Liquid Chromatography
RSD_r	Standard deviation for repeatability
RDS_R	Standard deviation for reproducibility
R_{Rec}	Recovery rate
RP-HPLC-UV	Reversed-Phase High Performance Liquid Chromatography coupled to Ultraviolet detection

Summary

An application was submitted to the Food Standards Agency in March 2021 from Huvepharma NV ("the applicant") for the new authorisation of an additive (amprolium hydrochloride-Coxam®), under the category of 'coccidiostats and histomonostats'. The additive is proposed to be used at doses of 500 mg/kg of complete feedingstuffs at 12% moisture, aiming to reduce parasitic infestation levels of *Eimeria spp*. in chickens for fattening and chickens reared for laying.

To support the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in evaluating the dossier, the Advisory Committee on Animal Feedingstuffs (ACAF) were asked to review the dossier and the supplementary information from the applicant.

The Committee evaluated the evidence provided by the applicant in the form of a report by the CVMP[2]. The original studies referenced in the report could not be accessed, therefore, the Committee was unable to conclude on the safety of the additive for consumers.

The views of AFFAJEG and ACAF have been taken into account in the safety assessment which represents the opinion of the FSA and FSS.

1. Introduction

The FSA and FSS have undertaken a risk assessment on the safety for consumers for a feed additive (amprolium hydrochloride - Coxam®, Huvepharma NV., Uitbreidingstraat 80, 2600 Antwerp, Belgium) requesting a new authorisation under retained regulation No 1831/2003[1] under the category of 'coccidiostats and histomonostats'.

To support the safety assessment by FSA and FSS, the ACAF provided advice to the FSA and FSS outlined in this document on the Safety for the Consumer section of the dossier.

In line with Article 8 of 1831/2003, the FSA/FSS assessment has considered whether the feed additive complies with the conditions laid down in Article 5, including: safety considerations for human, animal and environmental health; efficacy of the additive for its intended effect; potential impairment of the distinctive features of animal products. This, and the guidance put in place by EFSA for the evaluation of feed additive applications, has formed the basis and structure for the assessment.

With thanks to the members of the ACAF during the course of the assessment, who were: Professor Nicholas Jonsson, Martin Briggs, Professor Katrina Campbell, Susan MacDonald, Professor Matthew Fisher, Christine McAlinden, Dr. Donald Morrison, Derek Renshaw, Dr. Michael Salter, Dr. Adam Smith, Dr. Helen Warren and Dr. Nick Wheelhouse.

The dossier was evaluated by the ACAF at their December 2022 meeting.

This document outlines the discussion and conclusions of the AFFAJEG's assessment on the safety and efficacy of Coxam® as a feed additive.

2. Assessment

2.1. Additive

The additive is formulated containing the non-ionophore coccidiostat amprolium hydrochloride at a concentration of 250 g/kg, liquid paraffin at 30 g/kg and rice hulls up to 1 kg. The conditions of use proposed by the applicant are listed in Table 1. The

additive aims to reduce parasitic infestation levels of *Eimeria spp*. in chickens for fattening and chickens reared for laying.

Table 1: Proposed mode of use of amprolium hydrochloride (Coxam®)

Proposed mode of use in animal nutrition			
Additive		Amprolium hydrochloride	
CAS Number		137-88-2	
Category of additive		Coccidiostats and histomonostats	
Description			
Composition, description		**Formula**	**Method of analysis**
Preparation of amprolium hydrochloride		Containing no less than 237.5 g/kg and no more than 262.5 g/kg	Validated HPLC Method
Trade name (if appropriate)			Coxam
Name of the holder of authorisation (if appropriate)			-
Conditions of use			
Species or category of animal	**Maximum Age**	**Content in complete feedingstuffs (mg/kg)**	**Withdrawal period**
Chickens for fattening	-	500	-
Chickens reared for laying	12 weeks	500	-

2.2. Section III: Safety for the consumer

The applicant presented a Report from 2001 by the Committee for Medicinal Products for Veterinary Use[2] (CVMP, currently the Committee for Medicinal Products for Veterinary Use), as evidence to support the safety of the additive for consumers. The Secretariat had previously requested the applicant to provide the original documents referenced in the Report, but they could not be provided by the applicant. The Committee evaluated the Report, noting that the CVMP had established an acceptable daily intake (ADI) for amprolium hydrochloride of 0.1 mg/kg bw by applying an uncertainty factor of two hundred to the no observed adverse effect level (NOAEL) of 20 mg/kg bw/day established in a two-year rat toxicity study on the basis of suppressed bodyweight gain at higher doses. The large uncertainty factor had been used to compensate for the poor quality of the critical study. High variability was found between different species tested, and histopathology was performed on a low number of animals. The Committee concluded that the ADI proposed by the CVMP could not be confirmed without access to the original studies.

Several other studies looking at accumulation of amprolium in animal tissues are also summarised in the report. It was noted that, even if the ADI was to be accepted, no information was provided on distribution of residues to foodstuffs derived from target animals, making it impossible to estimate consumer exposure to amprolium residues and limiting the options to set maximum residue limits (MRLs) by risk managers. Given the impossibility to evaluate the study designs and their compliance with current guidance standards, the Committee could not conclude on the safety of amprolium hydrochloride for consumers.

2.2.1. Conclusions on safety for the consumer

The ACAF could not conclude on the safety of the additive for consumers.

3. Analytical methods evaluation

Conclusions on the analytical methods are presented here as an extract from the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of the Analysis for Coxam®[3]:

“For the quantification of amprolium in the feed additive (Coxam®), the Applicant submitted a single-laboratory validated and further verified method based on Reversed-Phase High Performance Liquid Chromatography coupled to Ultraviolet detection (RP-HPLC-UV). The following performance characteristics were reported: - a precision ranging from 0.8 to 1.0 %; and - a recovery rate (R_{Rec}) ranging from 99 to 100 %.

For the quantification of amprolium in the premixtures and feedingstuffs the Applicant submitted the ring trial validated Community method (Commission Regulation (EC) No 152/2009) based on Cation Exchange High Performance Liquid Chromatography coupled to Ultraviolet detection IE-HPLC-UV. The following performance characteristics were reported: - a relative standard deviation for repeatability (RSD_r) ranging from 1.9 to 5.0 % and a relative standard deviation for reproducibility (RSD_R) ranging from 3.0 to 6.5 %, - R_{Rec} ranging from 91 to 103 % and - a limit of quantification (LOQ) of 5 mg/kg feedingstuffs. In addition, the Applicant provided experimental evidence demonstrating the applicability of the Community method for determining amprolium in premixtures and feedingstuffs samples containing Coxam®.”

FSA/FSS accepts the EURL analytical method evaluation reports. FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

4. Conclusions

The Committee evaluated the report provided by the CVMP on the safety of the additive for consumers, but no access to the original studies was provided by the applicant. The ACAF could not conclude on the safety of the additive for consumers.

FSA/FSS accepts the EURL analytical method evaluation reports. FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

5. References

1. EC (European Commission), 2003. Regulation No 1831/2003 of the European Parliament and of the Council on additives for use in animal nutrition.

2. CVMP (Committee for Veterinary Medicinal Products), 2001. Amprolium. Summary Report. EMEA/MRL/767/00-FINAL. Available at: sumr¯P¯Amprolium _2_¯EMEA-MRL-767-00.doc (europa.eu)

3. EURL-FA (European Reference Laboratory for Feed Additives), 2016. Evaluation Report on the Analytical Methods submitted in connection with the Application for Authorisation of a Feed Additive according to Regulation (EC) No 1831/2003. Coxam. Available at: FAD-2016-0017 (europa.eu)

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