Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

EVANOVO Suspension and Solvent for Suspension for Injection for Chickens

Date Created: December 2022

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	EVANOVO Suspension and Solvent for Suspension for Injection for Chickens
Applicant	Laboratorios Hipra, S.A Avda. La Selva 135 Amer, 17170 Girona SPAIN
Active substance(s)	Attenuated *Eimeria acervulina*, strain 044 (598-809) Attenuated *Eimeria maxima*, strain 013 (352-476) Attenuated *Eimeria praecox*, strain 007 (235-317) Attenuated *Eimeria tenella*, strain 004 (221-299)
ATC Vetcode	QI01AN01
Target species	Chicken embryonated eggs
Indication for use	For the active immunisation of chickens to reduce clinical signs, intestinal lesions and oocysts output associated with coccidiosis caused by *Eimeria acervulina, Eimeria maxima, Eimeria praecox* and *Eimeria tenella.*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Centralised application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	20/10/2022

I. SCIENTIFIC OVERVIEW

This application was eligible for the centralised procedure under Article 3(2)(b) of Regulation (EC) No. 726/2004. It has been submitted in accordance with Article 12(3) of Directive 2001/82/EC as amended.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains sporulated oocysts derived from 4 precocious attenuated lines of *Eimeria* species: *Eimeria (E.) acervulina, E. maxima, E. praecox* and *E. tenella* and the excipients disodium phosphate dodecahydrate, polysorbate 80, potassium chloride, potassium dihydrogen phosphate, purified water and sodium chloride in the suspension and water for injections as an additional excipient in the solvent.

The container/closure system for the vaccine consists of Type I glass containers and closures with aluminium caps and the packaging of the solvent consists of polypropylene plastic bags. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains is justified.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method is based on the "seed lot system", as indicated in the general monograph of the Ph. Eur. 0062 (Vaccines for veterinary use). Antigens are disinfected and processed and production of the finished product involves mixing volumes of each strain with the excipients and then aseptically filling into vials.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substances are attenuated *Eimeria acervulina*, strain 044 (598-809); attenuated *Eimeria maxima*, strain 013 (352-476); attenuated *Eimeria praecox*, strain 007 (235-317) and attenuated *Eimeria tenella*, strain 004 (221-299), which are established active substances described in in-house monographs. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin used in production comply with the European Pharmacopoeia monographs or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur. Guidelines.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

The packaging complies with the Ph. Eur.

II.C.4. Substances of Biological Origin

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

The tests performed during production are described and the results of 3 consecutive, conforming to the specifications, are provided.

II.E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests are appearance, pH,

concentration of sporulated oocysts, concentration of sodium hypochlorite, detection of mycoplasmas, batch potency test, bacterial and fungal sterility and volume control.

The demonstration of the batch to batch consistency is based on the results of 3 consecutive batches. Other supportive data provided confirm the consistency of the production process.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

The in-use shelf-life of the diluted vaccine is supported by the data provided.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 12 months.
Shelf life of the HIPRAHATCH solvent as packaged for sale: 3 years.
Shelf life after dilution according to directions: 10 hours.
Shelf life after mixing with GUMBOHATCH: 2 hours.

EVANOVO suspension:

Store and transport refrigerated (2°C - 8°C).
Do not freeze.
Protect from light.

HIPRAHATCH solvent:

Do not store above 25°C.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of one dose, and an overdose in the target animal is demonstrated in a lab study where it was determined that vaccination with one dose or one overdose is safe when administered *in ovo* to SPF chickens. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines Ph. Eur.

No investigation of effect on reproductive performance was conducted because the vaccine is intended for short-lived chickens and there is no risk of use of the vaccine close to the onset of lay or during lay, given the route of administration.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study was not carried out.

For each live strain included in the vaccine (*Eimeria acervulina, Eimeria maxima, Eimeria tenella* and *Eimeria praecox*) specific studies were carried out to test

reversion to virulence and residual pathogenicity as per Ph. Eur. The studies conducted for each strain were: the performance of five passages in chickens with the attenuate coccidial master seed parasite (MSP) to obtain passaged material required to study reversion to virulence and to test for residual pathogenicity of the MSP and of passage 5 obtained in the other study. For all strains there was no evidence of an increase in virulence throughout the passages and no evidence of an increase in virulence, indicative of reversion, was seen in comparative testing between the MSP and the last MSP passage. The strains are suitable for use in a vaccinal strain since their attenuation is genetically stable.

Studies for spread, dissemination, biological properties, and recombination or genetic reassortment of the vaccine strains were not necessary and, therefore, not conducted.

The excipients used are allowed substances according to Table 1 of Regulation (EC) or are substances considered as not falling within the scope. Based on this information, no withdrawal period is proposed.

The interaction of the vaccine with GUMBOHATCH was studied. Two studies were conducted for safety and efficacy and in conclusion, when the vaccines are mixed prior to *in ovo* administration, it is safe.

Field studies

One GCP compliant multicentre field trial was conducted to assess both safety and efficacy of EVANOVO under field conditions. The study was a randomised, multicentre, double-blind, double-dummy, positive-controlled clinical field trial.

219,996 broiler chicken eggs, from which 207,820 chicks were hatched and included in the study. All eggs/chicks were vaccinated *in ovo* and at one day of age. The eggs at day 18 of incubation were randomly assigned to two treatment groups and received either the test product or the vaccine solvent only by means of *in ovo* vaccination. After hatching, at one day of age the test group chicks were vaccinated with a placebo and the positive control groups were vaccinated with a commercially available vaccine against coccidiosis via the oral route.

The animals underwent a follow up period until 41- 44 days of age, until the end of the fattening period in broiler chickens. During this period, adverse reactions, faeces appearance and mortality were monitored. Euthanasia and intestinal lesion scoring occurred on 15 animals per housing unit on days 7, 22, 28 and 35 and the animals body weight was recorded.

The evaluation of the safety of EVANOVO was based on hatching rate, body weight after hatching, body weight on day 22, intestinal lesion index on days 7 and 22 and adverse reactions. Any increase in mortality or change in faecal appearance were recorded separately to adverse events as they could also be considered in the assessment of efficacy.

There were no statistically significant differences in hatching rate between the groups. There was a statistically significant difference in body weight after hatching between groups. However, this difference was not considered to be clinically significant as there was no statistically significant difference between

the groups on day 22. The mean intestinal lesion index on day 7 was very low or nil in the positive control group and the test group respectively and was not statistically significant. Mean intestinal lesion index on study day 22 was lower in the EVANOVO group than in the positive control group, which was statistically significantly different; however, it is noted that this is not likely to be clinically relevant given the overall low mean score for intestinal lesion index score. No adverse reactions were observed during the course of the study and no changes in faecal appearance and no increase in mortality was observed.

In conclusion, the vaccine has shown to be safe.

Ecotoxicity

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that EVANOVO has no negative impact on the environment. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements.

Two studies were performed to investigate the efficacy of EVANOVO alone, one for the onset of immunity and one for the duration of immunity in addition to a laboratory study to investigate the efficacy of EVANOVO mixed with GUMBOHATCH.

Onset of Immunity

At 18 days of embryonation, one group of eggs was vaccinated *in ovo* with a minimum dose of EVANOVO and the other group was mock vaccinated with PBS. During the vaccination period, the eggs and chicks were all handled identically but the groups were separated after hatching. At 21 days of age, the chicks were randomly distributed into four groups and a challenge study was assigned to each group. The challenges were from each *Eimeria* species, and each test was an independent sub-study. For each challenge the animals were observed at least daily for 14 days post challenge.

The primary response variables included intestinal lesion score and weight/growth rate. Intestinal lesion scores were statistically analysed, and groups were compared. For *E. praecox*, macroscopic and microscopic lesions were analysed separately and combined. Growth rates and individual weights were analysed in the same way, but individual weights were compared.

The results from each species are as follows.

E. acervulina

Intestinal lesion score

A statistically significant change was found between the vaccinated (0.33) and control group (2.00).

E. maxima

Intestinal lesion score

A statistically significant change was found between the vaccinated (0.67) and control group (2.22).

E. praecox

Intestinal lesion score

A statistically significant change was observed between the vaccinated (0.72) and control group (1.61) for macroscopic changes. The microscopic evaluation showed a statistically significant difference between the vaccinated (mean score 0.83) and control group (mean score 2) for the mean parasitic score.

E. tenella

Intestinal lesion score

A statistically significant difference was found in intestinal lesion scores between the vaccinated (0.39) and control (2.83) group.

Weight

There was a statistically significant difference in growth rate was observed in each of the challenge studies, during the immediate post-challenge phase for *E. acervuline, E. maxima, E. praecox* and *E. tenella,* supporting that growth rate was greater in the vaccinated group during the acute challenge period.

Non-infected control

All parameters in the sentinel groups remained within normality. No lesions were observed and no clinical signs, no mortality and no oocysts were detected.

In conclusion, all the parameters indicated that the vaccine protected the animals. The results demonstrate efficacy of the administration of one dose when administered *in ovo* to 18 day old embryonated eggs.
The proposed onset of immunity is accepted at 21 days of age. The claims for reduction in intestinal lesions, clinical signs and oocyst output are supported at the claimed onset of immunity.
It is accepted that the growth rate in the vaccinated groups is significantly greater than in the control group.

Duration of Immunity

The study for duration of immunity was conducted in the same way as the onset of immunity study but was performed at 63 days of age.

The primary response variables and data analysis were the same as in the onset of immunity study above.

The results from each species are as follows.

E. acervulina

Intestinal lesion score

A statistically significant difference was found in intestinal lesion scores between the vaccinated (mean score of 0.25) and control (mean score of 2.92) groups.

E. maxima

Intestinal lesion score

A statistically significant difference was found in intestinal lesion scores between the vaccinated (0.25) and control (2.50) groups.

E. praecox

Intestinal lesion score

A statistically significant difference was found in intestinal lesion scores between the vaccinated and control group (mean lesion score was 0 in the vaccinated group and 1.25 in the control group). The microscopic evaluation showed a statistically significant difference between the vaccinated (mean score 0) and control group (mean score 1.83) for the mean parasitic score.

E. tenella

Intestinal lesion score

A statistically significant difference was found in intestinal lesion scores between the vaccinated (0.17) and control (3.75) groups.

Weight

A statistically significant decrease in growth rate was observed in the control group in the immediate post-challenge period following *E. acervuline, E. maxina* and *E. tenella* challenge or, in the case of *E. praecox,* slightly later (between days 4.5 to 14 for *E. praecox*).

Non-infected control

All parameters in the sentinel groups remained within normality. No lesions were observed, and no mortality and no oocysts were detected.

In conclusion, all the parameters indicated that the vaccine protected the animals. The results demonstrate efficacy of the administration of one dose when administered *in ovo* to 18 day old embryonated eggs. The proposed duration of immunity is accepted at 63 days of age following *in ovo* vaccination of 18 day old embryonated eggs. The claims for reduction in intestinal lesions, clinical signs and oocyst output are supported at the claimed duration of immunity. It is accepted that the growth rate in the vaccinated groups is significantly greater than in the control group.

Other Studies

A study was presented in which the efficacy of associated use was investigated. This study was to determine the efficacy of EVANOVO when combined with GUMBOHATCH.

The study was conducted in the same way as the onset and duration of immunity studies above except the vaccinated eggs were also administered GUMBOHATCH.

It was concluded that the mixed use of EVANOVO and GUMBOHATCH did not negatively affect the immunogenicity of EVANOVO.

Field Trials

One GCP compliant multicentre field trial was conducted to assess both safety and efficacy of EVANOVO under field conditions. The study is the same as the field study above under Safety.

The evaluation of the efficacy of EVANOVO was based on feed conversion rate (FCR). This index is a measure which directly related the weight gain during the fattening process; the higher conversion index means poorer performance.

There was no statistically significant difference in the FCR between groups with the mean values being very similar between the groups (1.56 for the test group and 1.57 for the positive control group).

Based on the results, it was concluded that EVANOVO is efficacious when administered *in ovo*.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product is favourable.

MODULE 4

POST- AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)