ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Hipracox Broilers Oral Suspension for Chickens

PuAR correct as of 07/11/2018 when RMS was transferred to IE.
Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0260/001/MR
Name, strength and pharmaceutical form	Hipracox Broilers Oral Suspension for Chickens
Applicant	Laboratorios Hipra, S.A. Avda La Selva, 135-17170 Amer(Girona) Spain
Active substances	*Eimeria acervulina* strain 003 *Eimeria maxima* strain 013 *Eimeria tenella* strain 004 *Eimeria mitis* strain 006 *Eimeria praecox* strain 007
ATC Vetcode	QI01AN01
Target species	Chickens (Broilers)
Indication for use	For active immunisation of broiler chicks to reduce intestinal colonisation, intestinal lesions and clinical signs of Coccidiosis caused by *Eimeria acervulina*, *E. maxima, E. mitis, E. praecox* and *E. tenella*. The onset of immunity is 14 days post-vaccination and the duration of protection is maintained at least for 42 days post-vaccination.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition decentralised procedure	25 June 2007
Date product first authorised in the Reference Member State (MRP only)	01 June 2006
Concerned Member States for original procedure	Austria Bulgaria Czech Republic Estonia Finland Germany Greece Hungary Ireland Italy Latvia Lithuania Netherlands Romania Slovakia Slovenia

I. SCIENTIFIC OVERVIEW

Hipracox Broilers is a live attenuated vaccine against avian coccidiosis. Coccidiosis is a debilitating, sometimes fatal disease caused by one or more of the seven species of *Eimeria* capable of parasitising the intestine of chickens. Hipracox Broilers is administered orally, in drinking water or hatchery spray mixed with uniflock diluent and no adjuvants or preservatives are present.

The life cycle of *Eimeria* involves some parasitic stages in the chicken and some free-living stages in the environment. *Eimeria* is excreted from the bird in the faeces in the form of oocysts. On excretion the oocyst is immature and must undergo a number of changes in the environment before it becomes infective again. A ripening stage known as sporulation occurs whereby sporozoites develop in the oocyst. When a bird ingests a sporulated oocyst the organism reproduces asexually and also sexually, by the fusion of male and female forms to form a zygote. These develop a coat around themselves and become another oocyst. Once excreted the cycle continues.

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. 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 of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains five strains of *Eimeria as the active*
Eimeria acervulina strain 003
Eimeria maxima strain 013
Eimeria tenella strain 004
Eimeria mitis strain 006
Eimeria praecox strain 007

Excipients:
Phosphate Buffered Solution (PBS): Potassium Chloride, Disodium Phosphate $12H_2O$, Potassium Dihydrogen Phosphate and Sodium Chloride

Colouring agent (UNIFLOCK®): Patent Blue V (E 131), Cochineal Red A Ponceau 4R (E 124) and Vanillin

The containers consist of glass vials with rubber stoppers and aluminium caps. The glass vials are colourless Type I vials of 10 ml (1,000 doses) or 50 ml (5,000 doses. The containers containing Uniflock are made of coloured glass. These are classified as Type II glass vials of 20 ml (1,000 doses) or 100 ml (5,000 doses). The particulars of the containers and controls performed are provided and conform to the regulation. The closures for both vaccine and diluent used consist of Type I polymeric elastomer closures. These comply with the requirements of the European Pharmacopoeia.

The choices of the vaccine strain and absence of preservative are justified.

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

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.

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

C. Control of Starting Materials

The active substance comprises the five strains of *Eimeria*, *Eimeria acervulina* strain 003, *Eimeria maxima* strain 013, *Eimeria tenella* strain 004, *Eimeria mitis* strain 006 *and Eimeria praecox* strain 007. Oocysts from each of the 5 strains were obtained from infected chickens from poultry farms in one European country. Chickens were inoculated with the original oocysts and further oocysts were then collected at specific times. After repeating this process, attenuated oocysts were obtained and collected from the faeces. Attenuated oocysts are maintained under constant conditions of temperature and aeration to induce sporulation, and are then chemically sterilised. After washing, they are mixed with a suitable storage medium and stored frozen until required. These stored oocysts are known as the master seeds.

Suitable tests have been carried out on the master seeds, including identity, sterility and freedom from avian leucosis, mycoplasmas and extraneous agents. Where the relevant version of the European Pharmacopoeia includes requirements for such tests, the requirements were met. In other cases, the company's own specification was used. All the organisms have been shown to lack virulence.

Starting materials of non-biological origin used in production comply with European pharmacopoeia monographs.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and 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.

E. Control tests during production

For each active ingredient (*Eimeria* antigen) tests performed during production are described and the results of three consecutive runs, conforming to the specifications, are provided.

F. 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 include appearance, pH, traces of sodium hypochlorite and potassium dichromate, fill

volume, viability of oocysts, detection of mycoplasmas, innocuousness, sterility and potency.

The demonstration of the batch to batch consistency is based on the results of six batches produced according to the method described in the dossier and on three batches of Uniflock. Other supportive data provided confirm the consistency of the production process.

G. Stability

Finished Product

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Stability data were provided by the company on three consecutive production batches of the vaccine, stored refrigerated for up to 9 months in the containers used for marketing. These data showed that the product remained stable for 9 months, therefore a 6 month shelf life was deemed appropriate when stored between 2 and 8°C. The product is not intended to be stored frozen. Data provided establishes the shelf-life for UNIFLOCK as 12 months.

In-Use

A complete container of the product is intended to be used all at once. Therefore stability data on partially used containers are not relevant. However, because the product is diluted in drinking water for administration, a study on its stability in drinking water was provided. This study considered a group of birds administered with the vaccine immediately after the contents of the vial had been diluted in drinking water (0 hours), and another group of birds vaccinated 24 hours after the vaccine had been diluted. There was no significant difference between these two groups of birds with regard to the excretion of oocysts. An in-use shelf-life not exceeding 10 hours for the medicated drinking water is justified. This is reflected in the SPC[1].

H. Genetically Modified Organisms

Not applicable

J. Other Information

Shelf life:

HIPRACOX® BROILERS:
Shelf-life of the veterinary medicinal product as packaged for sale: 6 months.
Shelf-life after first opening the immediate packaging: Use the vaccine immediately after opening and discard unused vaccine.
Shelf-life after dilution or reconstitution according to directions: it should not exceed 10 hours.

UNIFLOCK®:
Shelf-life as package for sale: 12 months.

[1] Summary of Product Characteristics

Special Precautions for Storage:
HIPRACOX® BROILERS:
Store and transport refrigerated (+2 - +8 ºC). Protect from light. Do not freeze.

UNIFLOCK®:
Store below 25ºC. Do not freeze.

III. SAFETY ASSESSMENT

Hipracox Broilers is intended to be administered orally to chickens as a single dose in the drinking water to protect them against avian coccidiosis. Data have been collected to demonstrate the safety of this vaccine.

Laboratory trials
The initial laboratory studies were conducted on one-day old coccidia-free chickens, the most sensitive of the target species. The vaccine was administered by oral gavage. Standard safety studies were conducted in accordance with Good Laboratory Practice and involved batches of high potency.

In the studies one-day old chicks were given either the normal dose, the normal dose repeated after 15 days, a dose of 10 times the normal dose or a dose of the product that contained no active substance for comparative purposes. The birds were observed daily and weight and food consumption were recorded up to 45 days. Faeces samples were collected for assessment of consistency and presence of oocysts. The results confirmed that a single dose, a repeated dose or a ten times overdose of Hipracox Broilers did not cause any clinical signs or attributable diarrhoea in coccidia-free day old chicks, and was not associated with adverse effects on production.
A study was conducted to determine whether Hipracox Broilers interfered with the efficacy of another vaccine against Newcastle Disease Virus (NDV). This was achieved by checking the antibody response of birds vaccinated with a single dose of Hipracox Broilers to subsequent vaccination against NDV. The results showed that there was no significant difference in the antibody results between birds vaccinated with Hipracox Broilers and those that were not. The study provided indicates that there is no reason to suspect that a live coccidial vaccine would cause immunosuppression.

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals.

For each live strain included in the vaccine:
In the case of live vaccines, it is necessary to consider factors such as whether the attenuated organisms used may revert to virulence[2] in use, whether they are disseminated within the bird, whether they may spread from bird to bird and whether they may react with other species of *Eimeria* to produce new harmful organisms.

[2] If an organism reverts to virulence, it regains the ability to cause disease.

With regard to the first of these possible effects, the company provided the report of laboratory trials for each strain, demonstrating that the properties of the oocysts did not change when the master seed oocysts were administered to chickens and the new oocysts excreted were administered to further chickens until five such passages had been completed.

Scientific arguments based on knowledge of the properties of various *Eimeria* species, indicate that the oocysts will not be disseminated (spread) within a vaccinated bird, as each parasite is specific for a particular region of the intestinal tract. It is expected that the vaccine organisms will spread from chicken to chicken. Indeed, this mechanism is important for the development of immunity in the flock. Chickens are the only birds that are susceptible to the *Eimeria* species used in the vaccine and there is therefore no possibility of spread to other species of bird.

Whilst it is possible that the vaccine organisms may interact with other species of *Eimeria* in field use, this can be prevented by proper cleaning of chicken houses between flocks, followed by populating the house with further vaccinated flocks. Any oocysts carried over between flocks are likely to have reduced virulence due to having reacted with the vaccine organisms.

Field studies

Field trials were carried out in accordance with Good Clinical Practice on a number of farms, all of which have previous histories of coccidiosis. The birds used in the trials at each site were all of the same genetic origin. At each site one group of birds received either Hipracox Broilers or a vaccination containing no active substances and then an anti-coccidial drug. The vaccine was mixed in the drinking water and the water left in troughs until it was consumed, as described in the recommendations for use. The results indicated that vaccination with Hipracox Broilers should cause no significant adverse effects.

Ecotoxicity

A discussion of the possible risks associated with the use of Hipracox Broilers has been provided. The parasite *Eimeria* is species specific and chicken coccidia do not infect other species. The production of oocysts is self limiting in that the numbers occurring in litter reduces over time. The vaccinal species are attenuated and have been shown not to revert to virulence. Hipracox Broilers does not pose a potential threat to the environment.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

A number of studies have been conducted on the efficacy of Hipracox Broilers.

Studies were carried out whereby the vaccine was administered to a group of one day-old coccidia-free chickens. At day 14 and day 42 the vaccinated birds were then exposed to virulent strains of the five species against which the vaccine is intended to protect. Weight and food consumption were monitored at intervals throughout the study and faeces samples were collected to permit the

estimation of oocyst output. At the end of the study *post mortem* examinations of the intestines were conducted on vaccinated birds that had received virulent *E. mitis* or *E. praecox* to assess whether they had been protected from damage by these organisms.

The data from this study showed that the onset of immunity occurred by day 14 after vaccination and continued until day 42, as evidenced by a reduction in oocyst excretion and in damage to the intestine.

Studies on the efficacy of each of the vaccinal strains in one-day old broiler chicks with and without maternal antibodies were also carried out. Both groups of chicks were vaccinated at one day of age and a virulent strain was administered at 14 days of age. Blood tests to detect the presence of antibodies against the specific strains were carried out. Results showed that the presence of maternal antibodies did not affect the vaccinal efficacy.

Another trial demonstrating efficacy in breeding birds whose blood was negative to the strains of *Eimeria* in Hipracox Broilers.

Field Trials

Two multicentric field trials were conducted to evaluate the safety and efficacy of the vaccine. This is described in section III. Evaluation of the efficacy was based on food conversion, oocyst counts, intestinal lesions, bird growth rates and mortality. The main observations were that coccidia were detected in the control group and none of the vaccinated birds had any signs of coccidial lesions, whereas some of the unvaccinated birds did. Also vaccinated birds excreted fewer oocysts by the end of the trial than unvaccinated birds. The results suggest that vaccination may have protected some birds from developing lesions of coccidiosis.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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)