IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Hipracox Broilers Oral suspension for chicken

PRODUCT SUMMARY

EU Procedure number	IE/V/0549/001 (formerly UK/V/0260/001)
Name, strength and pharmaceutical form	Hipracox Broilers Oral suspension for chicken
Active substances(s)	Eimeria acervulina, strain 003,Eimeria maxima, strain 013,Eimeria mitis, strain 006,Eimeria praecox, strain 007,Eimeria tenella, strain 004
Applicant	Laboratorios Hipra S.A. Avda. La Selva 135 17170 - Amer (Girona) Spain
Legal basis of application	Full application (Article 12(3) of Directive No 2001/82/EC)
Target species	Chickens
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.
ATCvet code	QI01AN01
Date of completion of the original mutual recognition decentralised procedure	25 June 2007 (UK) 31 October 2007 (IE)
Date product first authorised in the Reference Member State (MRP only)	01 June 2006 (UK)
Concerned Member States	Austria, Bulgaria, Estonia, Finland, Germany, Greece, Hungary, Ireland (RMS), Italy, Latvia, Lithuania, Netherlands, Romania, Slovakia, Slovenia UK added via RMS change

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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 closures for both vaccine and diluent used consist of Type I polymeric elastomer closures. These comply with the requirements of the European Pharmacopoeia.
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 at 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.
Suitable tests have been carried out on the master seeds. 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 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.

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. The approved shelf-life after dilution or reconstitution is reflected in the SPC.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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[1]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.

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.

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

IV. CLINICAL ASSESSMENT

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.