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 dw

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0275/001/MR
Name, strength and pharmaceutical form	Hipracox Broilers dw
Applicant	Laboratorios Hipra SA
Active substances	*Eimeria acervulina,* strain 003 300-390* *Eimeria maxima,* strain 013 200-260* *Eimeria mitis,* strain 006 300-390* *Eimeria praecox,* strain 007 300-390* *Eimeria tenella,* strain 004 250-325* *According to in vitro procedures of the manufacturer at the time of blending and at release.
ATC Vetcode	QI01AN01
Target species	Chicken (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*, *Eimeria maxima, Eimeria mitis, Eimeria praecox* and *Eimeria tenella*. The onset of immunity is 14 days post-vaccination and the duration of protection is maintained at least for 28 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 32(2) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	31 January 2008
Date product first authorised in the Reference Member State (MRP only)	23 May 2007
Concerned Member States for original procedure	Belgium Denmark France Norway Poland Portugal Spain Sweden

I. SCIENTIFIC OVERVIEW

Hipracox Broilers dw 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. Five antigens are present, *Eimeria acervulina, E. tenella, E. maxima, E. mitis* and *E. praecox.* The target species is broiler chickens with a claim to reduce intestinal colonisation and clinical signs of Coccidiosis caused by *Eimeria acervulina, E. tenella, E. maxima, E. mitis* and *E. praecox*. Hipracox Broilers dw is administered as a single dose, orally, in drinking water.

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 an exterior coat and become another oocyst. Once excreted the cycle continues.

The onset of immunity is 14 days post vaccination and the duration of protection is maintained for at least 28 days post vaccination. Minimum age for vaccination is 1 day old.

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be decided on a case by case basis.

No anticoccidial drugs or other agents having anticoccidial activity via feed or water should be used for at least 3 weeks following vaccination of the chickens. The correct replication of the vaccine oocysts and consequently, the development of a solid immunity could be hindered. Additionally, the enhancement of protection produced by oocyst re-infections would also be limited.

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[1]. 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 active antigens, *Eimeria acervulina, E. tenella, E. maxima, E. mitis* and *E. praecox* and the excipients potassium chloride, disodium phosphate $12H_20$, potassium dihydrogen phosphate and sodium chloride. The vaccine contains attenuated oocysts which are not capable of causing disease but are capable of inducing an immune response. The vaccine has been formulated to stimulate active immunity of broiler chickens, reducing infection, intestinal lesions and clinical signs of coccidiosis caused by *Eimeria acervulina*, *E. maxima, E. mitis, E. tenella,* and *E. praecox*.

The vaccine is a slightly brownish to white, turbid aqueous suspension containing between 1350 and 1755 oocysts per dose. The sporulated oocysts are suspended in concentrated form in phosphate buffered saline (PBS). The vaccine is given as sporulated oocysts in drinking water. This is presented in troughs and left available to the day old birds until it is drunk.

The vaccine is packaged in 10 ml and 50 ml Type I, colourless glass flasks with polymeric elastomer closures and aluminium flip-caps. The entire contents of the container are used at one time, therefore no antimicrobial preservative is included in the formulation.

[1] SPC – Summary of Product Characteristics.

The choice of the vaccine strain is 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 in accordance with Good Manufacturing Practice. A suitable quantity of master seed of each species is inoculated into separate groups of chickens to produce enough of each for a batch of finished product. The new oocysts are collected from the faeces, or in the case of *Eimeria tenella* from the intestine, at predetermined intervals and are treated in a similar way to the master seed except that at the end of the procedure they are not placed in storage medium. Instead, they are counted and the amount required for the product is calculated prior to mixing with a suitable amount of phosphate buffered saline. The process has been fully validated and appropriate tests are carried out during the procedure to ensure that the product contains the correct amount of sporulated oocysts and that it is free of undesirable agents.

C. Control of Starting Materials

Active Substance
The active substance comprises five strains of *Eimeria*. Oocysts from each of the five 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. The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

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.

Other Substances
The diluent of the active substances is saline solution, which is maintained at the correct pH by the addition of phosphate buffer. The ingredients of this solution and the substances used during the manufacturing process (not intended to be present in the finished product) are of an acceptable, specified quality.

Packaging Materials
The vaccine is packaged in 10 ml or 50 ml colourless type I glass flasks. These comply with the specifications set out in the European Pharmacopoeia (Ph. Eur.) monograph. The polymeric elastomer closures are type I and also comply with the Ph. Eur. monograph. A certificate of analysis has been provided.

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

Scientific data and certificates of suitability issued by the EDQM[2] 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

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

[2] European Directorate for the Quality of Medicines

F. Control Tests on the Finished Product

Appropriate tests are routinely conducted on the finished product, including appearance, pH, traces of sodium hypochlorite and potassium dichromate, fill volume, viability of oocysts, detection of mycoplasmas, innocuousness, sterility and potency

G. Stability

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. 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.

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[3].

CONCLUSIONS ON QUALITY

The company provided sufficient data to demonstrate that the production and control of starting materials, the production process and final product quality control are capable of ensuring a product that is of consistent quality.

III. SAFETY ASSESSMENT

Laboratory trials

The initial laboratory studies were conducted on one-day old coccidia-free broiler 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 dw 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 dw interfered with the efficacy of another vaccine against Newcastle Disease Virus (NDV).

[3] Summary of Product Characteristics

This was achieved by checking the antibody response of birds vaccinated with a single dose of Hipracox Broilers dw to subsequent vaccination against NDV. The results showed that there was no significant difference in the antibody results between birds vaccinated with Hipracox Broilers dw 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

In the case of live vaccines, it is necessary to consider factors such as whether the attenuated organisms used may revert to virulence[4] 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 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 dw 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 dw should cause no significant adverse effects.

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

Ecotoxicity

A discussion of the possible risks associated with the use of Hipracox Broilers dw 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 dw does not pose a potential threat to the environment.

CONCLUSIONS ON SAFETY AND RESIDUES

The safety part of the company's dossier fulfils the legislative requirements, and provides adequate information to assess the safety of the product.
The results from laboratory studies confirmed that a single dose, a repeated dose or a ten times overdose of Hipracox Broilers dw did not cause any clinical signs or diarrhoea in coccidia-free day old chicks, and was not associated with adverse effects on production. Field trial results indicated that vaccination with Hipracox Broilers dw should cause no significant adverse effects.

The vaccine contains no substances that represent a significant hazard to people administering it. However, it is recommended that people wash and disinfect hands and equipment after use. The affected area should be cleaned with soap and water in the case of accidental spillage onto the skin. Medical advice should be sought immediately and the package insert or label shown to the physician if accidentally ingested.

None of the ingredients of Hipracox Broilers dw are such as would cause unacceptable residues in meat from treated birds. There is no need for a withdrawal period[5] and no consumer safety concerns.

The product does not pose a potential threat to the environment.

IV CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

A number of studies have been conducted on the efficacy of Hipracox Broilers dw, these include studies using SPF[6] chickens.

Studies were carried out whereby the vaccine was administered in drinking water to a group of one day-old Ross broilers. 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.

[5] The withdrawal period is the period between the end of treatment and the time when birds may be killed for human consumption.
[6] SPF=Specific Pathogen Free

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

Field Trials

A field trial was 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.

CONCLUSIONS ON EFFICACY ASPECTS

The data available meet the regulatory requirements and permit an assessment of the efficacy of the vaccine. Laboratory and field data were presented which showed that the vaccine was effective in reducing infection and clinical signs caused by the five species of *Eimeria* in the product. Immunity commenced by 14 days after vaccination and continued until at least 42 days after vaccination. This is sufficient to cover the lifespan of broiler chickens.

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 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)