Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS
(Reference Member State)

REPEAT USE MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Paracox 5

PuAR correct as of 01/05/2018 when RMS was transferred to FR. Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0139/001/E01
Name, strength and pharmaceutical form	Paracox 5 Suspension for oral administration by dilution and spraying onto feed
Applicant	Schering-Plough Ltd Schering-Plough House Shire Park Welwyn Garden City Herts AL7 1TW
Active substances	*E. acervulina* HP *E. maxima* CP *E. maxima* MFP *E. mitis* HP *E. tenella* HP
ATC Vetcode	QI01AN
Target species	Chickens
Indication for use	For the active immunisation of broiler chickens to reduce infection and clinical signs of coccidiosis caused *by Eimeria acervulina, E. maxima, E. mitis* and *E. tenella.*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (**WWW.HEVRA.ORG**).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Repeat use 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	1st February 2006
Date product first authorised in the Reference Member State (MRP only)	June 1999
Concerned Member States for original procedure	Cyprus Czech Republic Estonia Hungary Latvia Lithuania Norway Poland Slovakia Slovenia

I. SCIENTIFIC OVERVIEW

Paracox 5 is a live attenuated vaccine incorporating four species of *Eimeria* that cause coccidiosis in domestic fowl. Coccidiosis is a debilitating, sometimes fatal disease caused by

one or more of the seven species of *Eimeria* which are capable of populating the intestine of chickens. Medication of chicken feed with anti-coccidial drugs has been a convenient and effective treatment, but resistance to these drugs has been reported, hence the need for a vaccine.

Eimeria have a complicated life cycle, with some, parasitic, stages in the chicken and some, free-living, stages in the environment. The stage which leaves the chicken, in the faeces, is known as an oocyst and this oocyst undergoes various changes before it is able to infect another chicken. These changes involve the process known as sporulation, which is a "ripening" stage in which sporozoites develop inside the oocyst. Once inside the chicken, the organism reproduces asexually and also sexually, by the fusion of male and female forms which, once fused to form a zygote, develop a coat around themselves to become another oocyst. This is then excreted and the cycle begins again.

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 slight 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 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 *Eimeria acervulina* HP; 500-650 oocysts, *Eimeria maxima* CP; 200-260 oocysts, *Eimeria maxima* MFP; 100-130 oocysts, *Eimeria mitis* HP; 1000-1300 oocysts, and *Eimeria tenella* HP; 500-650 oocysts. The product also contains the excipient phosphate buffered saline.

The vaccine contains attenuated oocysts which are not capable of causing disease but are capable of inducing an immune response. It has been formulated to induce active immunisation of broiler chickens to reduce infection and clinical signs of coccidiosis caused by *Eimeria acervulina* (abbreviated to *E. acervulina*), *E. maxima, E. mitis* and *E. tenella*. These species were chosen on the basis that they are either the most commonly occurring species in Europe or they cause the most severe disease, or both. Oocysts of two strains of *E. maxima*, are included in the product because this species does not induce a strong immune response and studies have shown that complete protection may not occur following vaccination with only one form. Thus, in total the product contains oocysts from 5 different *Eimeria*, hence the name Paracox 5.

The vaccine is a translucent, aqueous suspension containing 2,300 – 2,990 oocysts per dose. The oocysts are suspended in concentrated form in phosphate buffered saline (PBS)* and do not therefore need a suspending agent. The product needs to be shaken and diluted with water prior to administration as a spray on feed, in drinking water or as a hatchery spray.

---

[1] Summary of Product Characteristics
* PBS is saline which is maintained at the desired pH (degree of acidity) by the addition of sodium salts of phosphoric acid.

The product is available in two sizes, a 4 ml container containing 1000 doses and a 20 ml one containing 5000 doses. Because it is necessary to use the entire contents of a container at one time, no antimicrobial preservative is included in the formulation.

The container/closure systems are clear colourless polyethylene terephthalate copolyester (PETG) vials closed with bromobutyl stoppers and aluminium crimps. The particulars of the containers and controls performed are provided and conform to the regulation. There is no pharmacopoeial monograph for the aluminium crimps as these do not come into contact with the product.

The choice of vaccine strains 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 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.

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 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

The active substances are *E. acervulina* HP, *E. maxima* CP, *E. maxima* MFP, *E. mitis* HP and *E. tenella* HP, an established active substance. The active substances are manufactured in accordance with the principles of good manufacturing practice.

Oocysts of each organism were originally obtained from infected chickens. Because there is no way of attenuating or increasing the stock of oocysts except by administering them to the host bird, the original oocysts were inoculated into other chickens and more oocysts were collected from the birds at specific times. After several repetitions of this process, attenuated oocysts were obtained. Once attenuated oocysts had been obtained, future stocks were derived from a single oocyst of each species so that they would all have the same attenuation characteristics. Attenuated oocysts are treated 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 salmonellae, 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.

Starting materials of non-biological origin used in production comply with the companies in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur.[2] Monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the European Pharmacopeia; any deviation was adequately justified.

The diluent is saline solution, which is maintained at the correct pH by the addition of phosphate buffer. The ingredients of this solution and also other substances which are used during the manufacturing process but which are not intended to be present in the finished product are of specified quality.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control tests during production

The tests performed during production are described and the results of 3 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 in particular appearance, pH, sterility, potency, safety, and volume of vaccine in the vials.

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

G. Stability

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

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 52 weeks in the containers used for marketing. These data showed that the product remained effective for at least 33 weeks. Data derived from a fourth batch indicated that it remained effective for up to 47 weeks. On the basis of this

[2] European Pharmacopeia

information, and bearing in mind the need for a safety factor to be incorporated, a shelf life of 33 weeks was approved for the product when stored between 2 and 8°C. The product is not intended to be stored frozen.

A complete container of the product is intended to be used at the same time and therefore stability data on partially used containers are not relevant. However, because there will inevitably be a delay between spraying the product on to feed, and its being consumed by the birds, studies have been conducted to demonstrate how long it remains viable when in contact with feed. These demonstrated that the product remains efficacious for up to six hours after spraying. The usage instructions therefore recommend that birds should be given access to the feed within two hours of spraying so that a significant amount of feed will have been consumed before any deterioration in the product occurs.

In the case of administration in the drinking water, the diluted product is immediately available to the birds and studies have shown that it is drunk within 2 – 3 hours. However, since the active ingredients of the product are suspended in an aqueous solution, it would not therefore be expected that dilution in water would greatly affect their stability even if it took longer than 3 hours for the vaccine to be consumed.

H. 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

Paracox 5 is intended to be orally administered to chickens, at 1 – 3 days of age, to protect them from the common causes of coccidiosis. Oral administration may be achieved in three different ways, as a spray on feed, in drinking water or as a hatchery spray, and data have been collected to demonstrate the safety of each of these.

Laboratory and field studies have been conducted on the safety of the product in chickens and details of the batches used in these studies were provided.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal is demonstrated in two studies. Safety was assessed clinically, over an appropriate time course, through observation and physical examination. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

The initial laboratory studies investigating the safety of the product were conducted using the spray-on-feed method of administration. Two studies were conducted in which one-day-old chicks were given a single dose, an overdose or a repeated dose. Standard safety studies were conducted in accordance with Good Laboratory Practice and involved batches of the product at maximum potency, as a worst case situation.

In each study, one day-old chicks were given either the normal dose, a dose of ten times the normal dose, the normal dose repeated every four days for four administrations, or no dose at all.

Few adverse effects of the vaccine were observed. The vaccinated birds, particularly those in the overdose and repeated dose groups appeared to gain rather less weight than the birds given water only, and it was thought that this could be a result of the mild intestinal lesions which sometimes occurred. Paracox was shown to be safe even at substantial overdose levels.

An additional study was conducted in which birds were vaccinated by the hatchery spray method, incorporating cochineal (see Part IV of this report for further information on the reason for this). The results of this study confirmed that the addition of this red food colouring did not impact adversely on safety.

Effects on reproductive performance were examined: Studies on effects of the product on reproductive performance have not specifically been conducted with Paracox 5. However data generated using Paracox, a similar vaccine which contains oocysts from additional species, indicated a positive effect on reproductive performance, with improvements in uniformity, higher egg production and higher hatching rate. It is considered likely that Paracox 5 would have a similar effect. However, Paracox 5 is formulated for use in young chicks so effects on reproductive performance are not expected. Therefore this section of the SPC has the statement not applicable under it.

Two studies were conducted to investigate whether the product had any effect on the immune system of vaccinated birds. This was achieved by checking the antibody response of birds vaccinated with Paracox 5 to subsequent vaccination against infectious bursal disease (IBD), Newcastle disease (ND) and infectious bronchitis (IB). In a third study birds were vaccinated by the hatchery spray method and were then vaccinated against, IBD, IB or TRT (turkey rhinotracheitis). Overall, there was no significant difference in antibody responses between birds vaccinated with Paracox-5 and those not, although some female birds had a lower antibody response to IBD and IB. The studies provided sufficient assurance that Paracox 5 had no adverse effect on the immune response of vaccinated chicks to several other vaccines commonly used in chickens.

For each of the live strains included in the vaccine:
Specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strains.

With regard to the first of these possible effects, the company provided published information demonstrating the stability of oocysts such as those used in Paracox 5. This was supported by some experimental work 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 seven 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 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, it is possible to prevent this happening 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.

Based on these data the following has been included in the SPC.

Only vaccinate healthy birds. Do not administer to sick or stressed chicks, e.g. chilled, not feeding or drinking. 'Paracox 5' vaccine will not protect species other than chickens against coccidiosis and is only effective against *Eimeria* species indicated. 'Paracox 5' vaccine contains live coccidian and is dependant upon replication of the vaccinal lines within the host for development of protection. It is common to find oocysts in the gastrointestinal tract of vaccinated birds from 1-3 weeks or more after vaccination. These oocysts are most likely to be vaccinal oocysts which recycle in the birds via the litter. Recycling ensures satisfactory flock protection against all the pathogenic species of
Paracox-5 is for oral administration by spraying onto feed only. Chickens should be healthy and strictly floor reared on litter. Ensure that all vaccination equipment is thoroughly cleaned before use. Since all protection against coccidial infection following "Paracox 5" administration is enhanced by natural challenge, it should be noted that access to any therapeutic agents having anti-coccidial activity at any time following vaccination may reduce the duration of effective protection. This is important throughout the life of the chicken. To reduce the chance of coccidial field challenge before the onset of immunity, litter should be removed and chickens housing should be thoroughly cleaned between rearing cycles.

Paracox-5 contains no preservative or adjuvant therefore the proposed withdrawal period of zero days for chickens and any eggs produced by vaccinated chickens is acceptable.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Food and water provided at any stage before or after vaccination must be free from anti-coccidial agents including sulphonamides and antibacterial agents having anticoccidial activity. Do not mix with any other immunological product.

Field studies

Field trials under commercial conditions have been conducted using all mechanisms of administration to assess both the safety and efficacy of the product. In the case of administration as a spray on feed, four field trials have been conducted, two in the UK, one in France and one in Italy. The commercial premises where the birds were housed included some with and some without a history of clinical coccidiosis. At each site, some of the birds were treated with anti-coccidial drugs instead of being vaccinated, so that comparison of any effects could be made. Birds which received the vaccine did so via the spray-on-feed method at the recommended dose. The vaccine was of standard potency. Vaccination with Paracox 5 caused no adverse effects in any of the studies.

Two similar trials were conducted using the drinking water method of administration, and no adverse effects resulting from vaccination with Paracox 5 were observed.

A further two trials were conducted using the hatchery spray method of administration, and again no adverse effects resulting from vaccination with Paracox 5 were observed.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline. The major points made in this assessment are that the product consists of attenuated coccidial oocysts and phosphate buffered saline. The latter is of no environmental concern. The oocysts are species-specific and chicken coccidia do not infect other species. Furthermore, information is available to show that production of oocysts by cycling in the vaccinated birds is self-limiting, with the numbers occurring in the litter reducing over time. The litter is removed from the house when the flock is removed and any remaining oocysts would be destroyed by bacterial action, heat and ammonia within the compost. It is concluded that Paracox 5 does not pose a potential threat to the environment provided the disposal advice as stated on the SPC is followed.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

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 vaccine was well tolerated, with only very minor adverse effects when the vaccine was administered to chicks as a spray on feed or hatchery spray in laboratory studies. Field trials, in which the vaccine was administered by all three mechanisms, showed equivalence between these mechanisms and it was therefore not considered necessary to conduct laboratory studies for administration in drinking water.
The vaccine has also been shown to not adversely affect the development of immunity to other common vaccines, including those against infectious bronchitis, Newcastle disease, infectious bursal disease and turkey rhinotracheitis.

The vaccine contains no ingredients that represent a significant hazard to people administering it. However, it is recommended that people spraying the vaccine should wear well fitting masks and eye protection as it is clearly undesirable to inhale any product or to allow the spray to come in contact with the eyes.

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

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

* The withdrawal period is the period between the end of treatment and the time when birds may be killed for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

Several laboratory studies have been conducted on the efficacy of Paracox 5. Some of the earlier studies served to provide information which would enable the design of further studies to be optimised. Only the pivotal studies are discussed in this report.

Administration on Feed

In the pivotal study on administration of Paracox 5 in feed, vaccine was administered to one day-old Ross broilers via the spray-on-feed method of administration, using vaccine of minimum potency, as is usual for efficacy trials. The vaccinated birds were divided into groups and, at 14, 28 or 42 days after vaccination, were given a virulent strain of one of the four *Eimeria* species against which the vaccine is intended to protect. The birds were weighed at intervals throughout the study to assess growth rate, 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 which had received virulent *E. acervulina*, *E. maxima* and *E. tenella* to assess whether they had been protected from damage caused by these organisms. *E. mitis* does not cause such damage and therefore no *post mortem* examinations were carried out on birds which had received this species.

The data from this study showed that the onset of immunity occurred by day 14 after vaccination, and that by 28 days a significant level of protection is afforded, as indicated by a reduction in oocyst output and a reduction in the degree of damage to the intestine. The immunity continued for at least 42 days, the age at which broilers reach market weight. No correlation between vaccination and growth rate was found in this study.

Administration in drinking water

A similar study to the above was conducted to investigate the efficacy of the vaccine when administered in drinking water, using nipple drinkers fixed to in-line drinking systems. Apart from the means of administration, the major differences were that the vaccine was administered when the chicks were 3 days old, i.e. when they had learned to use the nipple drinkers, and they were exposed to virulent *Eimeria* 12, 26 or 40 days after vaccination.

The data from this study showed that the onset of immunity occurred from day 12 after vaccination, and that the immunity continues for at least 40 days.

Administration as a hatchery spray

Preliminary studies of this method of administration indicated that it was necessary to incorporate a colouring agent into the diluted vaccine before spraying. This colouring agent has two purposes - one is to identify those birds that have been sprayed, and the other is to improve uptake of the vaccine because of increased preening. The red food colouring agent cochineal (E120) was identified as being the most appropriate of several agents tested, one of its main advantages being that it is approved for food use. Thus the pivotal studies on efficacy of the vaccine when administered as a hatchery spray included cochineal. Apart from the method of administration, the design of the studies was basically similar to that of the studies of other mechanisms of administration, with vaccinated Ross broilers chicks being exposed to the vaccine at one day of age, and to virulent *Eimeria* 14, 28 or 42 days later.

The results of the study showed that immunity had developed by day 14, that it was optimal by day 28 and that it lasted until 42 days after vaccination. This was in line with the findings from experiments using other means of administration.

Field Trials

Administration on Feed

Four field trials have been conducted, two in the UK, one in France and one in Italy. The commercial premises where the broilers were housed included some with and some without a history of clinical coccidiosis. Some of the birds at each site were treated with anti-coccidial drugs instead of being vaccinated, so that comparison of any effects could be made. Birds which received the vaccine did so via the spray-on-feed method at the recommended dose. The vaccine was of standard potency. There was no incidence of coccidiosis in any of the birds in the study, and the vaccinated birds performed as well as birds given anti-coccidial drugs.

Administration in drinking water

In this case two field trials were conducted under commercial conditions, one in France and one in Italy. The commercial premises where the broilers were housed included some with a history of coccidiosis. The vaccine was administered exactly as described in the SPC. There was no incidence of coccidiosis in these studies, and the vaccinated birds performed as well as birds fed with anti-coccidial drugs under commercial rearing conditions.

Administration as a hatchery spray

Two field trials were also conducted in which the vaccine was administered as a hatchery spray, as described in the SPC. These trials took place in the UK and Italy. As in the case of the other two methods of administration, there was no incidence of coccidiosis in vaccinated birds, and these birds performed as well as birds treated with anti-coccidial drugs.

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)