Paul-Ehrlich-Institut

Beurteilungsbericht zur Veröffentlichung

(gemäß § 31 Abs. 2 Tierimpfstoff-Verordnung)

CIRBLOC

Zulassungsdatum:	30.03.2017
Zulassungsnummer:	PEI.V.11810.01.1
Datum der Erstellung des öffentlichen Beurteilungsberichts:	12.12.2017
Datum der Bekanntgabe beim Antragsteller der/des Zulassungsänderung/Widerrufs, Rücknahme, Anordnung des Ruhens der Zulassung:	

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(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CIRBLOC

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0270/001/DC
Name, strength and pharmaceutical form	CIRBLOC emulsion for injection for pigs
Applicant	CEVA-Phylaxia Veterinary Biologicals Co. Ltd. 1107 Budapest, Szállás u. 5. HUNGARY
Active substance(s)	Active substance per dose (2ml): Inactivated porcine circovirus (PCV) type 2b, strain Rm ≥ 1,100 AU* * Antigenic Units as determined in the in-vitro potency test (ELISA) Adjuvants per dose (2ml): Light liquid paraffin 157 mg Escherichia coli J5 LPS 2,500 – 38,000 EU** ** Endotoxin Units Preservative per dose (2ml) : Thiomersal 50 ug
ATC Vetcode	QI09AA07
Target species	Pigs for fattening
Indication for use	For the active immunization of fattening pigs from 3 weeks of age, to reduce viraemia, virus load in lymphoid tissues and virus shedding caused by porcine circovirus type 2 (PCV2) infection. To reduce weight loss associated with PCV2 infection during the fattening period. Onset of immunity: 3 weeks after vaccination Duration of immunity: 24 weeks after vaccination

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 32 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	21st December 2016
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Lithuania, Latvia, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Slovenia, Slovakia, United Kingdom

I. SCIENTIFIC OVERVIEW

Cirbloc is an inactivated vaccine containing porcine circovirus type 2 (PCV2b) antigens. The antigen is incorporated in an adjuvant for stimulation of immunity, based on a combination of light liquid paraffin and cell free *Escherichia coli* J5 LPS. Thiomersal is added as preservative.

The vaccine is supplied as an emulsion for injection.

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.

The product is safe for the user, the consumer of foodstuffs from treated pigs and for the environment, when used as recommended. Suitable 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. Qualitative and quantitative particulars

Cirbloc is an inactivated vaccine containing porcine circovirus type 2 (PCV2b) antigens. The antigen is incorporated in an adjuvant, based on a combination of light liquid paraffin and cell free Escherichia coli J5 LPS. Thiomersal is added as preservative.

The vaccine is supplied as an emulsion for injection.

Containers (vials) are composed of low density polyethylene without additives, the stoppers for the vials are composed of silicon coated nitryl rubbers and finally these are sealed with aluminium caps composed of aluminium in the lower part and plastic (polypropylene) in the upper part. Containers as well as stoppers are in accordance with the corresponding monographs of the European Pharmacopoeia.

The choice of the PCV vaccine strain and the adjuvant is justified.

As PCV2b has emerged as the most prevalent genotype in Europe this genotype was chosen as active substance. The vaccine virus is inactivated by using beta-propiolactone (BPL) as inactivation agent. The use of BPL is generally based on good experiences in the veterinary vaccine production

The adjuvant consists of 2 components: the mineral origin (oil) component and the biological origin (*Escherichia coli* J5 LPS) component. The use of mineral origin fraction, containing light liquid paraffin and esters of fatty acids and polyols, is based on the well-known experiences of these substances as general immune enhancer, has an established safety profile and is also used in other inactivated vaccines licensed in Europe. The biological origin fraction of the adjuvant contains non-toxic lipopolysaccharide (LPS) of *Escherichia coli* J5 strain. This *E. coli* J5 LPS as a component of the cell wall is produced by downstream processing of *E. coli* J5 culture following traditional fermentation techniques.

The vaccine as a multi-dose product and contains thiomersal as preservative which is widely used in veterinary vaccines.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

The product is an established pharmaceutical form for this type of vaccine, 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 (GMP) at a licensed manufacturing site. A corresponding manufacturing licence and GMP certificates are provided.

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

C. Control of Starting Materials

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 guidelines; any deviation was adequately justified.

Seed lots and cell banks have been produced as described in the relevant guideline.

Starting materials of non-biological origin used in production comply with relevant Ph. Eur. monographs or in-house specifications.

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.

D. Control tests during production

The tests performed during production conform to the relevant requirements; any deviation from these requirements is justified.

The tests include in particular: antigen quantification, inactivation control and sterility as well as *E. coli* LPS content, purity and sterility and, finally, filling volume. Test descriptions and the limits of acceptance are presented. The relevant test methods for in-process controls are satisfactorily validated. Results of three consecutive runs, conforming to the specifications, are provided.

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 include in particular: appearance, viscosity, type of emulsion, stability of emulsion, antigen quantification (potency and identity), *E. coli* LPS content, paraffin content, thiomersal content and sterility. Test descriptions and the limits of acceptance are presented. The relevant test methods are satisfactorily validated and the test specifications have been justified.

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

F. 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 (2 years) when stored under the approved conditions (2°C – 8°C).

The in-use shelf-life of the broached vaccine (10 hours) is supported by the data provided.

G. Other Information

Not applicable.

III. SAFETY ASSESSMENT

The following Ph. Eur. monographs and guidelines have been taken into account:

- Ph. Eur. Monograph 5.2.6 Evaluation of Safety of Veterinary Vaccines and Immunosera.
- Guidance on the safety testing of veterinary vaccines is provided by Directive 2001/82, Annex I, Title II as amended by Directive 2004/28/EC.
- Guideline on User Safety for Immunological Veterinary Medicinal Products - EMEA/CVMP/IWP/54533/2006
- CVMP guidance: “Environmental risk assessment for immunological veterinary medicinal products” (EMEA-CVMP/074/95, adopted 24 July 1996).
- Note for guidance: Field trials with veterinary vaccines - EMEA/CVMP/852/99 – FINAL –

Laboratory trials

Cirbloc is an inactivated vaccine for the active immunization of fattening pigs to reduce viraemia, virus load in lymphoid tissues and virus shedding caused by porcine circovirus type 2 (PCV2) infections and to reduce weight loss associated with PCV2 infection during the fattening period.

The vaccine is intended for intramuscular injection of fattening pigs from three weeks of age.

The trials have been performed in the target species (pigs).

The safety of the administration of one dose was demonstrated in two laboratory studies in 3-week-old piglets with low levels of MDA.

In each of these studies piglets were vaccinated once at three weeks of age; unvaccinated piglets were left as controls. Animals were observed for general health, rectal temperature, feeding behaviour and body weight gain. The injection site was observed after administration as well as post mortem.

Only mild local reactions were observed within the first day after vaccination, but no abnormal local or system reactions. A temperature increase was present six hours after vaccination in vaccinated animals compared to control animals which returned to baseline levels within 24 hours. No differences in body weight gain were observed between both groups.

The vaccine is indicated as a single dose vaccine for fattening pigs only therefore the safety of the administration of a repeated dose was not required.

The vaccine contains only inactivated antigen and thus the specific tests to be performed for live vaccines are not applicable.

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

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal. Therefore, specific tests on the impact of vaccination with Cirbloc on immunological functions of the pigs were not performed. Given the experience with the inactivated components of this vaccine, no adverse influences on the immune functions are expected.

The excipients used are considered to be safe because they are mentioned in Table 1 of Commission regulation 37/2010 requiring no MRL insert status with reference to MRL regulations. Based on this information, no withdrawal period is proposed.

No information is available on the safety 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 made on a case by case basis. An appropriate warning in the SPC is included.

Field studies

Four field trials were performed to evaluate the safety of the vaccine.

Briefly, a controlled field trial in France including piglets vaccinated once at three weeks of age and unvaccinated controls from which vaccinated and unvaccinated piglets were observed for safety parameters too. A temperature increase after vaccination was present. There was no abnormal systemic or local reaction. Some vaccinated piglets showed mild local reactions one day after vaccination. The weight gain was not significantly different between both groups.

The second field trial in Hungary included piglets vaccinated once at the age of three weeks and unvaccinated control animals. A temperature increase in vaccinated animals was observed. There were no abnormal systemic and local reactions observed. Some vaccinated piglets showed mild local reaction for 1 to 3 days after vaccination. The weight gain was significantly lower in the vaccinated group.

The third field trial was also performed in Hungary including piglets vaccinated once at three weeks of age and unvaccinated controls from which animals of both groups were used for individual safety observations too. In the vaccinated animals there was an increase of rectal temperature after treatment. The maximum increased temperature was four hours after vaccination which dropped down to baseline level within 24 hours after treatment. Some immediate reactions were observed in the vaccinated animals, e.g. consciousness collapse, vomiting or transient weakness. Also a few transient mild local reactions were observed in both groups with no significant difference.

The fourth field trial was also performed in Hungary and included piglets vaccinated once at the age of three weeks and unvaccinated controls from which again animals of both groups were used also for individual safety observations. No adverse event occurred during this study. No serious immediate, general or local reaction was observed. The vaccine had no negative effect on the performances of the animals. The increase of rectal temperature after treatment was significantly higher in the vaccinated group. The maximum increased temperature was noticed six hours after vaccination which dropped down to baseline level within 24 hours after vaccination. Some small transient local reactions were recorded in 10% of the vaccinated animals at the day of vaccination.

In the end, the vaccine was well tolerated under field conditions. Vaccination resulted in an increase in rectal temperature four to six hours after vaccination, but temperatures returned back to baseline levels within the one day. In up to 15% of the vaccinated animals minor local reactions were observed at the site of injection. Only mild immediate reactions were observed which resolved spontaneously. These slight reactions observed are indicated in the SPC.

The following overall conclusions can be drawn from the results of the safety studies:

- A transient mean increase in body temperature of approximately 1.5°C is very common on the day of vaccination as shown in safety studies. In individual cases the maximum increase may reach 2°C, but the body temperature returns to normal levels within 12-24 hours.
- A local reaction at the site of injection in the form of slight swelling and reddish colorization with a diameter up to 5 cm was very commonly observed during the safety studies, which lasts in general for not longer than three to four days. These reactions are of transient nature and do not need further treatment.
- Diarrhoea is very common post vaccination as observed in safety studies.
- Immediate, mild hypersensitivity-like reactions uncommonly occur after vaccination in studies resulting in transient clinical signs such as vomiting. These clinical signs normally resolve without treatment.

These local and systemic reactions observed are described in the SPC (Summary of Product Characteristics) and package leaflet under “adverse reactions” (section 4.6 and section 6, respectively).

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the Guidance “Environmental risk assessment for immunological veterinary medicinal products” (EMEA/CVMP/074/95, adopted 24 July 1996) which showed that no further assessment is required. The assessment concluded that all hazards identified have a negligible likelihood and therefore a Phase II assessment is not necessary.

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)

IV.B Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the following Ph. Eur. monographs and guidelines:

- Ph. Eur. 5.2.: Evaluation of efficacy of veterinary vaccines and immunosera
- Guidance on the efficacy testing of veterinary vaccines is provided by Directive 2001/82, Annex I, Title II as amended by Directive 2004/28/EC.

Vaccine batches used in the efficacy studies were produced as described in the dossier and met generally relevant release requirements.

The applicant performed two onset of immunity (OOI) studies in piglets with batches of two different formulations, a lower and a standard formulation. In both studies, the animals were challenged three weeks after vaccination using a PCV2b C1 virus. An onset of immunity of three weeks was sufficiently shown.

The duration of immunity (DOI) of 24 weeks was shown in one study performed again with two different vaccine formulations.

Additionally, two complementary studies were provided in which pigs were vaccinated in the field and then relocated for an experimental challenge infection after 4 weeks. These studies support the efficacy of Cirbloc with regard to reduction of viraemia, viral loads in lymphoid organs and virus shedding.

The influence of maternally derived antibodies on vaccine efficacy was evaluated by statistical analysis of results from field studies and the virological claims for the vaccine were still fulfilled even in the presence of high levels of MDAs. The degree of viraemia, shedding and viral loads in lymphoid organs was significantly decreased among vaccinated animals compared to control animals.

Field Trials

Three field trials were performed in Hungary and France, which support the claims for reduction of viraemia, viral loads in lymphoid organs and virus shedding.

Briefly, efficacy of vaccination was also demonstrated under field conditions in a controlled field trial in Hungary including piglets vaccinated once at three weeks of age and unvaccinated control piglets. A PCV2 field infection was confirmed by viremia between day 21 and 44. Vaccinated animals showed lower copy numbers of virus per millilitre serum compared to control animals and these lower titres were significantly lower on day 84 and day 111. Nasal shedding and virus load in lymphoid organs were shown to be significantly lower in vaccinated animals compared to control animals. No difference on weight gain was observed over the whole study period.

A second field trial performed in Hungary included again piglets vaccinated once at three weeks of age and unvaccinated control piglets. A PCV2 field infection was confirmed by virus copy numbers in serum samples which took place between week 6 and 9. It could be demonstrated that viremia, virus load in nasal swabs and lymphoid organs were lower in vaccinated animals compared to control piglets. A higher average daily weight gain was observed in the fattening period in vaccinated piglets.

A third field trial was performed in France and included piglets vaccinated once at three weeks of age as well as control animals. A PCV2 infection was observed between week 4 and 7 by analysing viral loads in serum samples. Viremia, nasal shedding and viral loads in lymphoid tissues were significantly lower in vaccinated animals. Differences in the average daily weight gains were found only between sexes and weaning batches.

In the end, the vaccine was shown to be efficacious under field conditions. The efficacy parameter of viremia, viral loads in lymphoid tissues and virus shedding were reduced in these field trials.

The following overall conclusions can be drawn from the results of the efficacy studies:

- For the active immunization of fattening pigs from 3 weeks of age, to reduce viraemia, virus load in lymphoid tissues and virus shedding caused by porcine circovirus type 2 (PCV2) infection. To reduce weight loss associated with PCV2 infection during the fattening period.
- Onset of immunity: Three weeks after vaccination.
- Duration of immunity: At least 24 weeks vaccination.

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.