09 September 2021
EMA/564312/2021
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Circovac (EMEA/V/C/WS1945)

Vaccine common name: Porcine circovirus vaccine (inactivated)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 20 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Ceva-Phylaxia Co.Ltd (the applicant), submitted to the European Medicines Agency (the Agency) on 29 January 2021 an application for a type II variation for Circovac and other related nationally authorised product, following a worksharing procedure.

1.2. Scope of the variation

Variation(s) requested		**Type**
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

To add the mixed, associated use (only piglets from 3 weeks of age) of the two vaccines (Circovac and Hyogen) and to extend the duration of immunity to 23 weeks in case of mixed use.

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 3 and Part 4

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Assessment

SPC and product literature

Mixed use was extensively described in sections 4.8 and 4.9 and the relative sections of the PI. In particular, the applicant amended the section 4.8 also with the sentence: "The data available are not sufficient to exclude the interaction of maternally derived antibodies against *Mycoplasma hyopneumoniae* with vaccine uptake (when Hyogen is used alone or in mix with Circovac). Interaction with maternal-derived antibodies is known and should be taken into consideration. It is recommended to delay vaccination in piglets with residual MDA against *Mycoplasma hyopneumoniae* at the age of 3 weeks".

The OOI is different between the single use and the mixed use being two weeks for the single use and three weeks for the mixed use. The DOI is 14 and 23 after the single use and the mixed use, respectively.

Although it is possible to consider this sentence pertinent to section 4.8 according to guideline EMA/CVMP/IWP/594618/2010, since there is a specific indication in the SPC guideline for section 4.9 ("The impact of maternally derived antibodies on vaccination should be stated, where applicable"), it was suggested to move the aforementioned sentence to section 4.9.

The proposed amendment provides a clear indication of OOI and DOI after mixed use of Circovac with Hyogen.

Although the OOI is different between the single use and the mixed use (two weeks for the single use and three weeks for the mixed use), this difference can be considered acceptable due to the fact that the product Hyogen has a OOI of 3 weeks and the applicant provided evidence of the onset at three weeks after the mixed use. However, since there is a different DOI for the product used alone (14 weeks) and combined (23 weeks), the applicant commits to harmonise the PIs with a variation to extend the DOI for Circovac to 23 weeks, including estimated timelines.

Quality

The applicant provide data to support the negligible effect on the stability of the single components when used associated. The major risk with the mixing of different emulsions is to create a new emulsion of lower quality (e.g. reduced stability, higher viscosity). The Applicant has conducted technical studies in order to compare the physico-chemical properties of the mixed vaccine to the ones of the individual IVMPs.

Safety

Safety of combined administration of Hyogen and Circovac in three-week-old piglets

The study was carried out under GLP conditions.

The study was conducted using 20 recently weaned piglets of approximately 21 days of age on Day 0. There were 10 piglets on each of the two treatments, each receiving either test or control items, respectively, by intramuscular injection.

Clinical Observations, rectal temperatures, injection site reactions were recorded. All pigs were euthanised on day 14 after vaccination and histopathological examinations were carried out.

Overall, after the associated vaccination an increase of body temperature and swelling in the injection site were recorded.

Field safety of associated administration of Hyogen and Circovac in three-week-old piglets

60 commercial piglets of 3 weeks of age were enrolled in the study. 29 were vaccinated and 31 were kept as control. Primary parameters to be assessed to verify safety were: general health, rectal temperature and local reactions. The secondary parameter was weight gain.

The results showed that there were no differences between vaccinated and control piglets.

Overall, the trial showed that the adverse reactions of the associated use are not different from those observed with the single use of the products.

Efficacy

EFFICACY OF ASSOCIATED USE OF HYOGEN AND CIRCOVAC VACCINE AGAINST *M. HYOPNEUMONIAE* INFECTION

Onset of immunity of Circovac-Hyogen RTM in 3 week-old pigs against *M. hyopneumoniae* challenge

The objective of this study was to demonstrate the onset of immunity of Hyogen vaccine, representing the minimum protective dose (MPD), when combined with Circovac in one injection (ready to mix; RTM) against a heterologous *Mycoplasma hyopneumoniae* challenge.

50 piglets seronegative for *Mycoplasma hyopneumoniae* were enrolled. At 3 weeks of age, 25 were vaccinated with a standard dose for Circovac and minimum protective dose for Hyogen and 25 were kept as control. Challenge with *M. hyopneumoniae* was performed at 6 weeks of age (3 weeks after vaccination).

Primary parameters were lung lesions, scored in accordance with the Ph. Eur. monograph 2448 ("Porcine Enzootic Pneumonia vaccine (Inactivated)". Supportive parameters to evaluate efficacy were morbidity (assessed by dyspnea, rattle, cough), weight gains (for information only) and antibody response to the vaccine (only for information).

Lung lesions

The distribution of the lung lesion scores is shown in Figure 1. Lung scores were significantly different in vaccinated group (group 1) versus control group (group 2) (p= 0.0000, Wilcoxon rank-sum test).

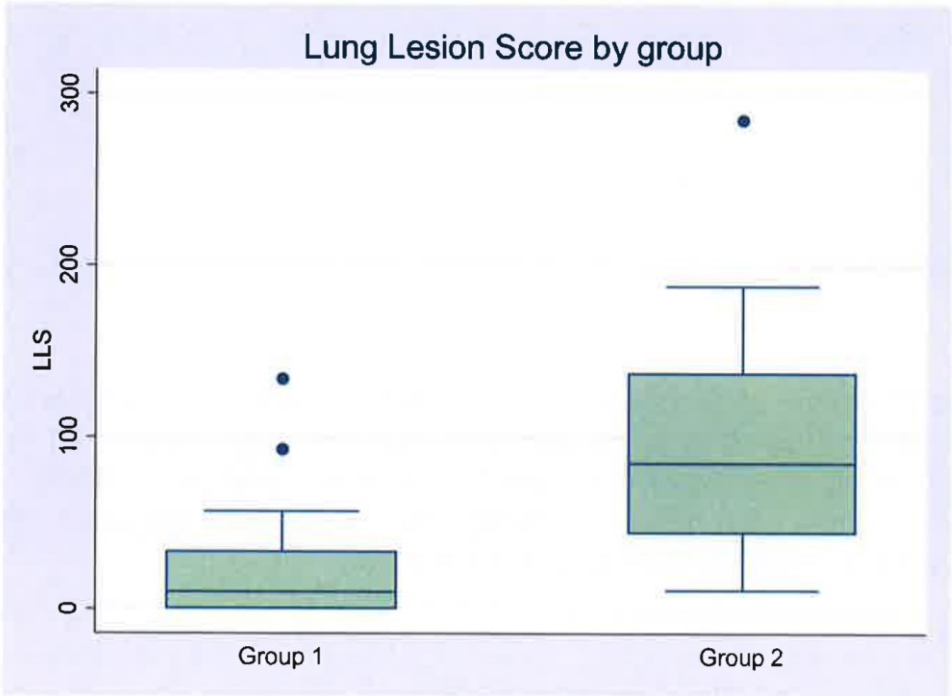


Figure 1. Weighted lung lesion scores

Body weight gain

No significant differences in body weight gain or rectal temperature were found between the groups.

The applicant concluded that the associated use of the products does not interfere with the efficacy of Hyogen versus *M. hyopneumoniae* infections.

The results of the trial support the efficacy of the associated use of the products against *M. hyopneumoniae* infections with an onset of 3 weeks after vaccination.

Twenty three weeks duration of immunity of Circovac+Hyogen RTM against *M. hyopneumoniae* challenge

The objective of this study was to demonstrate the duration of immunity of Circovac+Hyogen RTM against *M. hyopneumoniae* challenge against a heterologous *Mycoplasma hyopneumoniae* challenge.

55 piglets seronegative for *Mycoplasma hyopneumoniae* were enrolled. At 3 weeks of age, 27 were vaccinated with a standard dose and 28 were kept as control. Challenge with *M. hyopneumoniae* was performed at 26 weeks of age (23 weeks after vaccination).

Primary parameters were lung lesions, scored in accordance with the Ph. Eur. monograph 2448 ("Porcine Enzootic Pneumonia vaccine (Inactivated)". Supportive parameters to evaluate efficacy were morbidity (assessed by dyspnea, rattle, cough), weight gains (for information only) and antibody response to the vaccine (only for information).

Lung lesions

Results and Conclusion according to the main study parameter:

	Group 1	Group 2
Vaccine applied	Circovac + Hyogen	Control
mean lung score	33.2	72.3

Lung scores were significantly different in vaccinated group (group 1) versus control group (group 2).

Regarding secondary parameters, no significant differences were found for the mean of the clinical scores after challenge between the groups, while the mean daily body weight gain was significantly higher in Group 1 than in Group 2.

The results of the trial support the efficacy of the associated use of the products against *M. hyopneumoniae* infections with a duration of 23 weeks after vaccination.

Overall, the efficacy assessment of associated use of Hyogen and Circovac vaccines against *M. hyopneumoniae* infection has been provided, according to the requirements of Directive 2001/82/EC as amended and guideline EMA/CVMP/IWP/594618/2010 "Requirements for combined vaccines and associations of immunological veterinary medicinal products" and EMEA/CVMP/682/99 "Note for Guidance: Duration of protection achieved by veterinary vaccines". No field trial was performed. The applicant claims that the results from the conducted clinical studies are fully supportive.

Overall, the results of the clinical trials support the efficacy of the associated use of the products against *M. hyopneumoniae* infections with a duration of 23 weeks after vaccination. The applicant's position regarding the lack of field test was supported.

EFFICACY OF ASSOCIATED USE OF HYOGEN AND CIRCOVAC VACCINE AGAINST PORCINE CIRCOVIRUS TYPE 2 INFECTION

Efficacy study of Circovac Hyogen RTM (Ready to Mix) vaccines in pigs against PCV2 challenge 3 weeks after vaccination

The objective of this study was to demonstrate the onset of immunity of Circovac vaccine combined with Hyogen in one injection, against a challenge infection with PCV2, 3 weeks after vaccination. The

Circovac vaccine was administered at a dose of 1.5 $\log_{10}$ OD_{50} antigen.

30 piglets of 3 weeks of age were enrolled, divided in two similar groups (vaccinated and controls). Since the challenge with PCV2 under laboratory conditions usually does not result in significant clinical signs, the following parameters were used to evaluate the efficacy of the vaccine:

- Viraemia
- PCV2 load of the selected lymphoid tissues (tonsil, mediastinal, mesenterial and inguinal lymph nodes) by either PCR or immunohistochemistry
- virus shedding (nasal and faecal swabs)

Secondary study parameters were body weight gain difference between vaccinated and non-vaccinated animals during the post-challenge observation period and antibody response to PCV2.

A significant difference was found between the vaccinated group (Circovac and Hyogen, RTM) and the control group in terms of viremia (p=0.0200).

A significant reduction of the PCV2 viral load was observed between the vaccinated group and the control group in tonsils, mediastinal and inguinal lymph nodes (p=0.0245, p=0.0310 and p=0.0381, respectively).

No significant reduction of the PCV2 viral load was seen between the vaccinated group and the control group in mesenterial lymph nodes (p=0.8143).

Regarding virus shedding from nasal swabs, although no significant difference was observed when comparing the Area under the curve (AUC), a significant difference was observed between the vaccinated group and the control group on Day 35 (2 weeks post challenge) (p=0.0291).

Although no significant difference was observed when comparing the Area under the curve (AUC) on virus shedding from faecal swabs, significant differences were observed between the vaccinated group and the control group on Day 42 and 49 (3 and 4 weeks post challenge) (p=0.0059 and p=0.0001 respectively).

The histological analysis of the lymph nodes and tonsils showed no lesions characteristic for PCV2 (hyperplasia, lymphocyte depletion and presence of syncytial giant cells) in any of the samples (score 0: absence of lesions). Therefore, these parameters were not evaluated statistically.

The immunohistochemistry (IHC) of the lymph nodes and tonsils showed significant difference between the vaccinated group and the control group regarding immunohistochemistry scores in the tonsils, mediastinal, mesenterial and inguinal lymph nodes (p=0.0188, p=0.0009, p=0.0130 and p=0.0031, respectively).

No significant difference was found between the groups regarding the body weight gain from D-1 to D21 and from D21 to D49 (p=9.9332 and p=6.3219, respectively).

No statistically significant difference was found between the PCV2 antibody levels of the vaccinated group (Circovac and Hyogen, RTM) and the control group before challenge (D-1, D21) and D2B (7 dpch) (pto.os for all timepoints). Following vaccination the average antibody titer was similar between the two groups, but following challenge there was a clear difference in the immune response, as shown by the strong antibody titer increase in the vaccinated group (indicating booster effect), compared to the low/almost absent increase in titer in the controls.

Overall, the results of the clinical trial support the efficacy of the associated use of the products against PCV2 infections with an onset of 3 weeks after vaccination.

Duration of immunity of 23 weeks after immunisation of 3 weeks old piglets with Circovac + Hyogen RTM (ready to mix) or Circovac alone followed by challenge with a PCV2 strain

And

Duration of immunity of Circovac Hyogen RTM (ready to mix) in fattening pigs (18-week-long DOI) challenged with PCV2

Cumulatively, the two studies performed (23 weeks DOI and 18 weeks DOI) evaluated the duration of immunity of Circovac against PCV2 infection if mixed with Hyogen and applied to 3-week old piglets. Animals were challenged intranasally at 18 or 23 weeks after vaccination respectively. The results summarized in the following table including legend and footnotes:

= not significant comparing vaccinated pigs to non-vaccinated pigs
= significant comparing vaccinated pigs to non-vaccinated pigs
= "neutral" - significant differences observed pre- and post-challenge

Indications/claims	Study A-RA2/S/2114/19 – DOI 23 weeks	Study DV-198-2019 – DOI 18 weeks
Maternally derived antibodies	**low to moderate levels**	**low levels**
Reduction of faecal excretion of PCV2		
Reduction of nasal excretion **		
Reduction of viral load in blood	low number of positive samples	low number of positive samples
Reduction of viral load in lymphoid tissues (PCR)	tonsils mesenterial ln. (mediastinal ln. *)	in all lymphoid tissues tested
Reduction of lesions in lymphoid tissues		
Reduction of PCV2-linked clinical signs	not evaluated	
Reduction of wasting, weight loss	scale out of order at the end of the study	differences pre- and post-challenge
Reduction of mortality	not evaluated	not evaluated

* only significant for pairwise comparison (Group 1 vs 2 and Group 2 vs. 3)
** evaluated but no indication/claim in the SPC

Results of study 23 weeks DOI did not show adequately efficacy of the mixed use of Circovac and Hyogen against PCV2 challenge infection 23 weeks after vaccination. As depicted in the table above the majority of efficacy claims have not been supported by the study. In addition, results of study evaluating the DOI of 18 weeks after vaccination against PCV2 challenge infection only support the claims for reduction in viral loads in lymphoid organs and in faecal excretions.

Furthermore, it should be kept in mind that the results of these studies will be provided to support the extension of the DOI of Circovac alone in a future variation procedure. Further, in study evaluating the DOI of 18 weeks after vaccination the validity criterion – above 80% of the animals in

the control group should have a positive PCR score in all tissues after challenge - was not met. In addition, it is noted that the applicant himself defined requirements (see subitem "Efficacy pass criteria" and "Assumptions made for proof of efficacy") which should be passed when comparing vaccinated pigs to non-vaccinated pigs:

a) lower incidence/ significant reduction of viremia

b) lower incidence/ significant reduction of the viral load at least in one lymphoid tissue (by either PCR or immunohistochemistry)

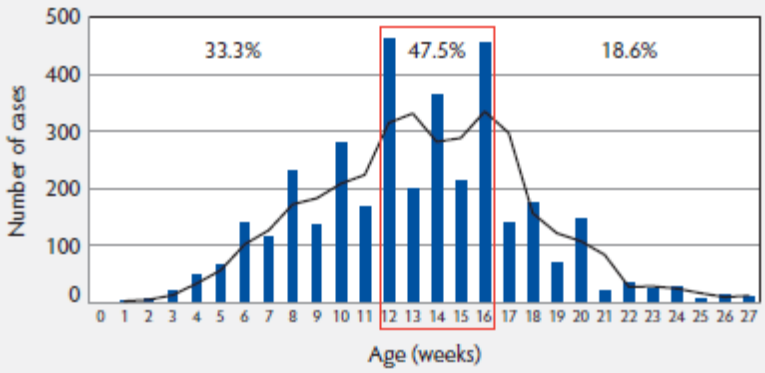
c) lower incidence/ significant reduction in virus shedding.

These requirements are only partly fulfilled. However, it is noted that results obtained after vaccination with Circovac alone or Circovac mixed with Hyogen were comparable in both studies and animals had low levels of maternally derived antibodies.

Approved indication of Circovac was not confirmed in the referred studies in its entirety but besides the reduction of virus load in the lymphoid tissues, in study 23 weeks DOI the nasal and the faecal virus shedding were also reduced even if the faecal virus shedding not significantly. In study 18 weeks DOI the faecal shedding was reduced significantly with the virus load in the lymphoid tissues though the nasal virus shedding was not supported due to its non-detectability in all groups.

The lack of differences between groups can be attributable to the age-dependent susceptibility to the PCV2-linked clinical signs, including wasting, weight loss and mortality as verified in the frame of a large-scale survey conducted by Hui-Gang Shen (Hui-Gang Shen et. al., 2012).

Figure 2. Numbers of porcine circovirus associated disease cases at different pig ages submitted to the Iowa State University Veterinary Diagnostic Laboratory, Ames, Iowa, between 2003 and 2010. The black line represents a trend line and was added to account for the apparent bias in recording even weeks rather than odd weeks on the submission form. The age of the pigs was expressed in rounded weeks with the exception of pigs ≥ 27 weeks of age, which were classified as 27 weeks old. The percentages represent the numbers of cases 0-11 weeks of age (1209 cases; 33.3%), 12-16 weeks of age (1694 cases; 47.5%, red frame), and 17-27 weeks of age (662 cases; 18.6%).



Indication of Circovac was not entirely confirmed in the provided information and the applicant justified this lack of statistically significant evidence on the basis of the age-dependant evolution of the host pathogen interplay. The studies 23 weeks DOI and 18 weeks showed that the challenge infection did not exert a severe effect neither in control groups. It means that the possibility to discriminate the efficacy between the vaccinated (single or mixed) and the control groups is markedly reduced. Nevertheless, it is possible to extrapolate that either the single or the mixed use provided a

coherent tendency for efficacy inducing a reduction of virus load in lymphoid tissues and a reduction in shedding (different degree in nasal and faecal swabs). Overall, taking into consideration that the disease has different clinical patterns in animals of different age, it is acceptable to consider the claims still valid, even if not completely justified as done in younger animals.

3. Scientific Overview

Circovac, presented as emulsion and suspension for emulsion for injection, contains inactivated Porcine Circovirus 2 (PCV2) and it is intended to induce active immunisation of piglets, as well as gilts and sows (to provide passive immunity in piglets) to reduce faecal excretion of PCV2 and virus load in blood, and as an aid to reduce PCV2-linked clinical signs, including wasting, weight loss and mortality as well as to reduce virus load and lesions in lymphoid tissues associated with PCV2 infection. In the SPC the onset of immunity is specified with 2 weeks and the duration of immunity with 14 weeks after vaccination.

The variation pertains the associated use (only piglets from 3 weeks of age) of Circovac and Hyogen (Hyogen is an inactivated vaccine, containing *Mycoplasma hyopneumoniae* strain 2940 as active substance, and light liquid paraffin and cell free *Escherichia coli* J5 LPS as adjuvant). Such associated use has an onset and duration of immunity of 3 and 23 weeks, respectively.

4. Benefit-risk assessment of the proposed change

Circovac is an inactivated vaccine composed of a suspension containing porcine circovirus type 2 (PCV2) antigen and an emulsion containing an oily adjuvant (o/w). It is intended to stimulate active immunity in gilts and sows to provide passive immunity in piglets, or for active immunisation of piglets. Vaccination of piglets is recommended from 3 weeks of age by one shot of a dose (0.5 ml) in order to reduce faecal excretion of PCV2 and virus load in blood, and as an aid to reduce PCV2 linked clinical signs, including.

The proposed variation is to add the mixed, associated use (only piglets from 3 weeks of age) of the two vaccines (Circovac and Hyogen) and to extend the duration of immunity to 23 weeks in case of mixed use.

Benefit assessment

Direct therapeutic benefit

The benefits of the associated use of the products relies upon a reduction of stress induced by handling animals for vaccination.

4.1. Risk assessment

Quality:

Quality of the products is not affected.

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

The administration of Circovac in accordance with SPC recommendations is generally well tolerated. The associated use with Hyogen does not modify the safety of the product.

Risk for the user:

The CVMP concludes that the user safety for this product and its associated use in combination with Hyogen is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

Risk for the environment:

Circovac and its associated use in combination with Hyogen is not expected to pose a risk for the environment when used according to the SPC recommendations.

Risk for the consumer:

No additional risk for the user arises from the associated use of the products.

Special risks:

No additional risks arise from the associated use of the products.

4.2. Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product and its associated use with Hyogen, relevant to the piglets, users, environment and consumer and to provide advice on how to prevent or reduce these risks.

User safety:

No additional risk for the user arises from the associated use of the products.

Environmental safety:

No additional risk arises from the associated use of the products.

4.3. Evaluation of the benefit-risk balance

The benefit-risk balance is positive.

5. Conclusion

Based on the original and complementary data presented on safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Circovac is approvable.

Changes are required in the following Annexes to the Community marketing authorisation:

I and IIIB

Please refer to the separate product information showing the tracked changes.

As a consequence of this variation, the sections 4.8, 4.9 and 6.2 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.