7 December 2017
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Suvaxyn Circo (EMEA/V/C/004242/0000)

Common name: porcine circovirus vaccine (inactivated, recombinant)

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

The applicant Zoetis Belgium SA submitted on 24 February 2017 an application for a marketing authorisation to the European Medicines Agency (the Agency) for Suvaxyn Circo, through the centralised procedure under Article 3(1) of Regulation (EC) No 726/2004 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 4 June 2015 as Suvaxyn Circo is developed by means of a recombinant DNA technology.

The product is a recombinant vaccine containing an inactivated recombinant chimeric porcine circovirus type 1 containing the porcine circovirus type 2 ORF2 protein. The applicant applied for the following indication: active immunisation of pigs from 3 weeks against porcine circovirus type 2 (PCV2) to reduce viral load in blood and lymphoid tissues and faecal shedding caused by infection with PCV2. The product is administered as a 2ml dose by the intramuscular route (IM) in the neck behind the ear.

The product is presented in high density polyethylene vials of 50 ml, of 100 ml and of 250 ml (25, 50 and 125 doses) in pack sizes of 1 vial (50 ml, 100 ml and 250 ml), 4 vials (250 ml) and 10 vials (250 ml).

The rapporteur appointed is Frédéric Klein and the co-rapporteur is Ellen-Margrethe Vestergaard.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC (full application).

On 7 December 2017, the CVMP adopted an opinion and CVMP assessment report.

On 7 February 2018, the European Commission adopted a Commission Decision granting the marketing authorisation for Suvaxyn Circo.

Scientific advice

Not applicable.

MUMS Status

Not applicable

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (version 1.4 dated 18 Mar 2015) which fulfils the requirements of Directive 2001/82/EC was provided. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The manufacturing site of the PCV antigen is Zoetis Charles City site (Iowa, US) for both the parent and the fall-out product. The manufacturing site of the finished product is Zoetis Louvain-La-Neuve site (Belgium) for both the parent and the fall-out product. The site for the quality control of the finished product and batch release for both the parent and the fall-out products is Zoetis Louvain-La-Neuve site.

Both Zoetis Louvain-La-Neuve and Zoetis Charles City have been recently inspected with positive outcome and have a valid manufacturing authorisation. Certificates of GMP compliance were provided for both sites. The most recent GMP inspections (with positive outcome) were performed on 21 October 2016 (Zoetis Charles City) and 19 January 2017 (Zoetis Louvain-La-Neuve).

A GMP declaration for the active substance(s) manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by the manufacturing site responsible for batch release which has taken into consideration the GMP certificate available for the active substance site issued by of the competent authorities of Belgium (Zoetis Louvain-La-Neuve) and the UK (Zoetis Charles City) following inspection.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of the active substance(s) and of the finished product manufacturing sites has been satisfactorily established and is in line with legal requirements.

Part 2 - Quality

Chemical, Pharmaceutical and Biological/Microbiological information (Quality)

Qualitative and quantitative particulars of the constituents

Qualitative and quantitative particulars

The qualitative and quantitative composition per 2 ml dose of Suvaxyn Circo liquid vaccine is given below.

Suvaxyn Circo liquid vaccine composition: liquid vaccine composition: recombinant porcine circovirus type 1 expressing porcine circovirus type 2 ORF2 protein (2.3-12.4 RP), squalane (0.4%), poloxamer 401 (0.2%), polysorbate 80 (0.032%), EDTA tetrasodium (46.8 µg), disodium tetraborate decahydrate (0.4 µg), thiomersal (0.0085-0.0115%) and PBS.

The composition of PBS solution (composition per mL) is: sodium chloride (8.5 mg/ml), disodium phosphate anhydrous (0.55 mg/ml), monobasic potassium phosphate anhydrous (0.08 mg/ml) and water for injection.

Container & closure

The vaccine is presented in 25 doses (50 ml), 50 doses (100 ml) or 125 doses (250 ml) presentations which are respectively filled into 50, 100 and 250 ml high density polyethylene vials (compliant to Ph.Eur.). Each vial is closed with a pharmaceutical grade rubber stopper and sealed with an aluminium cap. The containers and closure systems are the same as for the parent vaccine Suvaxyn Circo+MH RTU.

Product Development

Suvaxyn Circo is a monovalent vaccine intended for use in pigs aged 21 days or older, containing inactivated recombinant chimeric porcine circovirus type 1 containing the porcine circovirus type 2 ORF2 protein.

Zoetis already has a central Marketing Authorisation (MA) for a monovalent inactivated PCV2 vaccine (SUVAXYN PCV), which contains the same antigen, but a different adjuvant (SLCD).

Suvaxyn Circo is a 'fall out' vaccine closely related to Suvaxyn Circo+MH RTU. The only essential difference is that Suvaxyn Circo does not contain the *M hyopneumoniae* antigen. Suvaxyn Circo and Suvaxyn Circo+MH RTU are manufactured at the same production sites. The starting materials and the container and closure system of Suvaxyn Circo are the same as for the parent vaccine. Manufacturing of active substance is identical to that of the parent vaccine. Manufacturing of finished product is identical except that no *M. hyopneumoniae* antigen is added.

The vaccine strain was constructed by cloning the ORF2 capsid gene from a PCV2 strain into a non-pathogenic PCV1 genome. In this chimeric construct, PCV2 capsid gene itself is avirulent and non-infectious, and the PCV1 genome backbone is non-pathogenic as well. The PCV antigen is inactivated using betapropiolactone (BPL) as inactivation agent. BPL completely degrades without leaving residues in the final product after inactivation. Kinetics of inactivation studies were conducted. Sampling for inactivation kinetics was conducted at hourly intervals following the first BPL addition for inactivation kinetics. Intermediate time point sampling for in-vivo and in-vitro completion of inactivation tests were collected at 24 (prior to second BPL addition), 48, 56, 64, 72, 80 and 108 hours. During the course of the inactivation process, samples were assayed for infectious cPCV1-2 content, osmolarity, total protein and pH. The results obtained on concentrated samples at the different intervals have shown that no live virus was detected after 72 hours (or not more than 67% of the inactivation process used during manufactured i.e. 108-120 hours). In addition, in order to provide assurance that inactivation is complete with high titre starting material, live concentrated bulk was further concentrated to 60x and inactivated with 0.4% BPL. The starting titre of the 60x concentrated cPCV1-2 was 8.4 log10 TCID50 per ml. The rate of inactivation with the first 0.2% addition of BPL over the first 8 hours was found to be 0.44 log10 TCID50 per ml per hour. No infectious cPCV1-2 was detected by the in-vivo and in-vitro inactivation tests after 72 hours.

Each 2 ml of vaccine contains recombinant porcine circovirus type 1 expressing porcine circovirus type 2 ORF2 protein, with a relative potency between 2.3 and 12.4. The 2 ml dosage and IM route of administration are routinely used for swine vaccines and were chosen for this vaccine as well. The minimum and maximum relative potencies were validated using laboratory efficacy and safety studies.

The adjuvant is squalane, which is incorporated in SP oil, also known as Metastim, a mixture which also contains poloxamer 401 and polysorbate 80. The antimicrobial preservative used in the formulation of the vaccine is thiomersal.

Description of the manufacturing method

Production of cPCV1-2 antigen

The cPCV1-2 strain is grown on PK-15 cells. The cell cultures may be passaged up to MCS + 19 ready for production. The Working Seed Virus (WSV) is inoculated into the cells which are then planted into the bioreactors for growth on microcarriers. Up to four harvests of the virus may be collected. The microcarriers are removed from the viral fluids by filtration. Batches of antigen are made within 7 passages from the Master Seed. Antigen harvests (one lot or more) are concentrated between 10-30 fold by filtration. The concentrated virus stocks are inactivated using 0.4% Betapropriolactone (BPL). The viral fluids are then neutralised with sodium thiosulphate (NMT 0.1M final) and mixed prior to sampling for testing. An inactivation kinetics study was conducted to validate the process of inactivation for the cPCV1-2 antigen. The viral fluids are dispensed into containers (polypropylene bags or stainless steel vessels) and may be stored at 2-8 °C for up to 24 months.

Production of finished product

The required amount of PCV antigen is blended to reach a release potency within the specifications. More than one batch of PCV antigen may be used to formulate a vaccine batch. The excipients (including SP oil and thiomersal) are added to the final formulation. The batch size for the finished vaccine is from 200 to 2000 litres. The bulk vaccine is continuously stirred and aseptically filled into the HDPE vials. The vials are closed with the sterile siliconised rubber stoppers and sealed with the aluminium caps.

Production and control of starting materials

Starting materials listed in pharmacopoeias

An overview is given of all starting materials listed in a Pharmacopoeia : foetal bovine serum, D-glucose anhydrous, gentamicin sulphate, hydrochloric acid, phenol red sodium salt, potassium chloride, potassium phosphate monobasic anhydrous, purified water, sodium chloride, sodium hydrogen carbonate, sodium hydroxide, sodium phosphate dibasic anhydrous, sodium phosphate dibasic heptahydrate , sodium dihydrogen phosphate monohydrate, sodium thiosulfate pentahydrate, water for injections, disodium tetraborate decahydrate, hydrochloric acid concentrated, polysorbate 80, squalane and thiomersal.

Certificates of Analyses (CoAs) were provided demonstrating compliance to the respective European Pharmacopoeia (Ph. Eur.) monographs or U.S. Pharmacopeia (USP). There is also reference for phenol red sodium salt to American Chemical Society (ACS) grade.

Excipients (thiomersal, PBS and EDTA listed separately in section below)

Starting Material	Reference to Standard
Bovine Serum * *(Foetal Bovine Serum)*	Ph. Eur. 2262
D-Glucose, Anhydrous *(Dextrose)*	Ph. Eur. 0177
Gentamicin Sulfate	Ph. Eur. 4640
Hydrochloric Acid	Ph. Eur. 0002
Phenol Red Sodium Salt	ACS **
Potassium Chloride (for PCV antigen)	Ph. Eur. 0185
Potassium Phosphate Monobasic Anhydrous (for PCV antigen)	Ph. Eur. 0920
Purified Water	Ph. Eur. 0008
Sodium Chloride (for PCV antigen)	Ph. Eur. 0193
Sodium Hydrogen Carbonate	Ph. Eur. 0195
Sodium Hydroxide (for PCV antigen)	Ph. Eur. 0677
Sodium Phosphate Dibasic Anhydrous (for PCV antigen)	Ph. Eur. 1509
Sodium Phosphate Dibasic Heptahydrate	USP
Sodium Dihydrogen Phosphate Monohydrate *(Sodium Phosphate Monobasic)*	USP
Sodium Thiosulfate Pentahydrate	Ph. Eur. 0414
Water for Injections (for PCV antigen)	Ph. Eur. 0169
Disodium tetraborate decahydrate	Ph. Eur. 0013
Hydrochloric Acid, Concentrated	Ph. Eur. 0002
Polysorbate 80 * *(Montanox 80, Tween 80)*	Ph. Eur. 0428
Potassium Chloride (for final vaccine)	Ph. Eur. 0185
Potassium Phosphate Monobasic Anhydrous (for final vaccine) *(Monobasic potassium phosphate)*	Ph. Eur. 0920
Sodium Chloride (for final vaccine)	Ph. Eur. 0193
Sodium Hydroxide (for final vaccine)	Ph. Eur. 0677
Sodium Phosphate Dibasic Anhydrous (for final vaccine) *(Disodium phosphate anhydrous)*	Ph. Eur. 1509
Squalane *	Ph. Eur. 1630
Thiomersal	Ph. Eur. 1625
Water for Injections (for final vaccine)	Ph. Eur. 0169

*Starting material of biological origin

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin are: porcine circovirus, PK-15 cell line, lactalbumin hydrolysate, microcarriers, OptiMEM 50x salts II solution, porcine trypsin powder, foetal bovine serum, polysorbate 80 and squalane.

Information on these biological materials has been provided, including detailed information on the PK15 master cell seed and the cPCV1-2 master seed lot.

Starting Material	Biological Origin
Porcine Circovirus	Porcine
PK-15 Cell Line	Porcine kidney
Lactalbumin Hydrolysate (LAH)	Bovine (milk) and porcine pancreas (Enzymes of porcine origin are used in the Production of the material)
Microcarriers	Gelatin from pig skin
OptiMEM 50x Salts II Solution (contains transferrin)	Bovine blood
Porcine Trypsin Powder	Porcine pancreas and bovine milk (for lactose)
Bovine Serum (Foetal Bovine Serum)	Bovine blood
Polysorbate 80 (Montanox 80, Tween 80)	Oleic acid (Vegetable or Porcine/Bovine)
Squalane	Shark liver

Stability of active substance (PCV antigen)

A 27 months real time stability program has been carried out on three antigen batches stored at +2 °C to +8 °C. The stability test results were acceptable and show that the antigen remains stable over a period of 27 months when stored at +2 °C to +8 °C.

Starting materials of non-biological origin

Starting materials of non-biological origin that are not listed in a Pharmacopoeia are: betapropiolactone, EMEM with phenol red, EDTA tetrasodium, OptiMEM 50x acid soluble solution, OptiMEM 50x salts and poloxamer 401.

In house preparation of media and solutions consisting of several components

Detailed qualitative and quantitative composition, method of preparation and storage of the media and solutions prepared in-house are provided.

Details on the composition of SP oil, thiomersal solution and PBS are provided.

PBS solution (composition per mL)

Name	*Quantity / 1 mL (MP236)*	*Quantity / 1 mL (2x concentrated – MP238)*	*Reference*
Sodium chloride	8.5 mg	17 mg	Ph. Eur. 0193
Disodium phosphate anhydrous	0.55 mg	1.1 mg	Ph. Eur. 1509
Monobasic Potassium Phosphate anhydrous	0.08 mg	0.16 mg	Ph. Eur. 0920
Water for Injections	*qsp* 1 mL	*qsp* 1 mL	Ph. Eur. 0169

The vaccine has been investigated in respect of the starting materials as defined in section 2 of the combined CPMP/CVMP "Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMA/410/01/Rev.3). The starting materials of animal origin used in the production of the final product comply with the current

regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.3) and Commission Directive 1999/104/EEC.

Starting materials of animal original for which one or more materials does not have an EDQM certificate available, but scientific data demonstrating compliance with the Note for Guidance have been submitted are listed below:

Starting Material	Animal Origin	TSE Compliance
Porcine Circovirus	Porcine	Exempt – Porcine origin
PK-15 Cell Line	Porcine	Exempt – Porcine origin
Bovine serum	Bovine	R1-CEP 2005-087 R1-CEP 2000-387 R1-CEP 2000-076 R1-CEP 2000-211 R1-CEP 2000-384 R1-CEP 2001-083
Lactalbumin hydrolysate (LAH)	Bovine Milk	Exempt - Bovine milk suitable for human consumption
	Porcine pancreas	Exempt – Porcine origin
Microcarriers	Gelatin derived from Pig skin	Exempt – Porcine origin
Optimem Salt II Solution containing Transferrin	Bovine blood	R1-CEP 2000-410
Polysorbate 80	Tween 80 – Animal origin not specified	R1-CEP 2001-079
Porcine trypsin powder	Porcine pancreas	Exempt – Porcine origin
	Lactose from bovine milk	Exempt – Bovine milk suitable for human consumption
Squalane	Shark liver	Exempt – Fish origin

Control tests during the manufacturing process

Harvested antigen fluids before inactivation are tested for: identity, sterility and virus titre.

Inactivated antigen is tested for: completeness of inactivation, residual sodium thiosulfate, protein content (Bradford), sterility and ELISA potency (virus content).

The description of the methods and summaries of the validations were provided.

Batch data were provided for 4 batches of PCV antigen; all results were compliant with the specifications.

Control tests on the finished product

The description of the methods used for the control of the finished product and the specifications were provided. The finished product is tested for: description, PCV potency/identification, squalane quantification, thiomersal content, sterility, pH and dynamic viscosity.

The potency test is performed by sandwich ELISA using polyclonal antibodies to PCV. The bound protein is detected using a specific monoclonal antibody and the immune complex is visualized using a

colorimetric substrate. The antigen content is calculated by interpolation on the reference curve and expressed in Relative Potency (RP). Acceptance criterion: between 2.3 and 12.4 RP.

Batch-to-batch consistency

The specifications proposed at release and at the end of shelf-life are appropriate to control the quality of the finished product. The results of the analysis of three consistency batches of the lowest dose (25 dose presentation) and of the highest dose (125 dose presentation) of the finished product were presented. All test result complied with the required specifications.

Stability

A 39 months real time stability program has been initiated on 6 batches (corresponding to 3 different blending bulks filled in 25 and 125 dose presentations) stored at +2 °C to +8 °C. The stability testing program was presented. One blend was targeting a low RP, while the other 2 blends targeted a higher-RP.

The study is currently on-going and results for up to 11-12 months of storage are available to date; all results were within respective specifications. The stability indicating parameters are stable and highly similar to those of the parent vaccine (indicating that the absence of the Mycoplasma antigen has no impact on the vaccine's stability).

The vaccine Suvaxyn Circo+MH RTU vaccine, which is already approved, has a shelf-life of 18 months. The current vaccine Suvaxyn Circo only differs from Suvaxyn Circo+MH RTU vaccine by the absence of the MH antigen, whereas the PCV antigen is stable at 2-8 °C for at least 27 months (no decrease or trend in potency observed). These findings support the proposed shelf life of 18 months for the Suvaxyn Circo finished product.

No in-use shelf life data were provided by the applicant since it is indicated that the vaccine is recommended for use immediately after first opening the immediate packaging.

Overall conclusions on quality

The applicant has provided detailed information on the vaccine's composition, the manufacturing process, the starting materials, the analytical methods and control tests for active substance and finished product. Also batch data and stability data were provided. QC release test results showed that the product is compliant to its specifications.

The applicant has adequately addressed the concerns that were raised. All questions have been resolved.

In conclusion, information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. Based on the review of the data on quality, the manufacture and control of Suvaxyn Circo are considered acceptable. The applicant is requested though to take into account the recommendation regarding the stability of the finished product.

Recommendation: The applicant should provide the 21 months stability data of the finished product as soon as it becomes available. Moreover, regardless of the approach for the previously approved parent vaccine, it is expected that at the final time point the sterility of the product and container closure integrity will be tested for 3 stability batches.

Part 3 – Safety

Introduction and general requirements

Five (5) laboratory and five (5) field safety studies were performed with Suvaxyn Circo+MH RTU in accordance with Ph. Eur. monograph 0062 on Vaccines for veterinary use and/or Ph. Eur. monograph 5.2.6 on Evaluation of safety of veterinary vaccines and immunosera. Moreover, the laboratory trials were reported to have been conducted in accordance with Good Laboratory Practice (GLP) requirements and field studies in compliance Good Clinical Practice (GCP). This was acceptable as Suvaxyn Circo+MH RTU has been centrally approved and contains both PVC2 and *M. hyopneumoniae.*

Vaccinations were performed in accordance with the proposed vaccination scheme and administration route: IM single vaccination of 2 ml from 3 weeks of age. The health status of the animals included in the studies was tested individually and no data on the herd were provided.

Safety documentation

Laboratory tests

Safety of the administration of one dose and of an overdose

The safety of the administration of one dose and of an overdose of vaccine was evaluated in a total of 36, 17-22 -day-old crossbred piglets (the most sensitive category of target species) which were seronegative for PCV2 and *M. hyopneumoniae* before vaccination. The animals sourced from a holding where no recent clinical history of infection by *Haemophilus parasuis*, porcine reproductive and respiratory syndrome virus (PRRSV), *M. hyopneumoniae* and porcine circovirus (PCV) was recorded. Two (2) groups of 12 pigs each were treated IM respectively with 1 dose of Suvaxyn Circo+MH RTU at the maximum potency (PCV of 6.42 RP and *M. hyopneumoniae* of 3.84 RP) and a double dose of the same batch of Suvaxyn Circo+MH RTU; 1 group of 12 pigs was kept as unvaccinated control and was administered with saline solution.

Animals were monitored over 28 days. No clinical signs and no impact on growth were reported. However, transient increase in body temperature was very common during the first 28 hours after vaccination. Two (2) piglets, one from each group reported local reaction at the site of injection in form of swelling areas not exceeding 2 cm of diameter and disappearing within 2 days. At the end of the observation period microscopic analysis of the injection site, showed in all pigs minimal to moderate lymphocytic and macrophagic inflammation, in some cases associated to multi nucleated giant cells and minimal fibroplasias.

In another study twelve 3-day old piglets were vaccinated twice within an interval of 14 days with Suvaxyn Circo+MH RTU in the neck region (1st administration left, - 2nd administration right). The vaccine contained antigens higher than the upper threshold (PCV of 12.45 RP and *M. hyopneumoniae* of 6.75 RP). Both the antigen content (higher than the upper limit) and the age of the vaccinates (3 days-old instead of 3 weeks of age) represented a worst case scenario. The temperature increased by an average of 0.2 °C and 0.8 °C respectively. However, although general reactions were stronger at the 2nd injection, the local reaction was lighter and there was no impact on the body weight gain and macroscopic aspect of the injection site 28 days after vaccination.

Two other US studies were performed with a 2x overdosed vaccine.

In first study, thirty nine (39) clinically healthy piglets were enrolled at the minimum recommended age, e.g. 3 weeks (18-23 days). The piglets were vaccinated with 3 different 2x batches of Suvaxyn Combo Circo + MH RTU (3.4 to 5.28 PCV2 RP and 2.45 to 3.02 *M. hyopneumoniae* RPs). A transient pyrexia (fever) was observed in one animal from 2 different groups over the 2 days after vaccination as well as diarrhoea in one animal in control and in one vaccinated groups. Mild swelling at injection site was reported in 1 animal which resolved by day 2 after injection.

In second study, twenty (20) clinically healthy piglets were enrolled younger than the minimum recommended age, e.g. 12-13 days of age. The piglets were vaccinated with a 2x batch of Suvaxyn Combo Circo + MH RTU (4.70 PCV2 RP and 2.45 *M. hyopneumoniae* RP). A transient pyrexia (fever) in 3 vaccinated animals over the 2 days after vaccination. Neither other general signs nor injection site reactions were reported.

Information on the safety profile of the vaccine were collected also from one efficacy laboratory study where 3 pigs reported mild hypersensitivity-like reactions such as vomiting , or depression after vaccination. Since the vaccine was administered at weaning those symptoms might be due to physiological induction of cortisol secretion and intestinal modification that frequently cause diarrhoea in piglets, however a differential diagnosis with anaphylactic reactions needs to be taken into consideration and a proper warning have been included in the SPC.

In conclusion, results showed that the administration of a single dose of Suvaxyn Circo+MH RTU is considered safe. Adverse reaction such as limited local reactions, transient increase in temperature and potential anaphylactic reaction are adequately addressed in the SPC.

Safety of the repeated administration of one dose

A study was provided aiming at investigating the safety of the repeated administration of one dose of Suvaxyn Circo+ MH RTU in 16-20-day old pigs. A total of 24 piglets were enrolled in the study. A group of 12 pigs was administered the vaccine 2 times IM, 14 days apart. A group of 12 pigs was left unvaccinated as control group and saline solution was administered. The farm from where the piglets came and piglets' characteristics, as well as the vaccine batch was similar to the previous study. Rectal temperature was significantly higher after the first injection but not after the second. No other general reactions were reported. There was no difference in weight gain between vaccinated and control pigs during a one-month observation period. Local reactions were observed in the 17% (2 out of 12) of the vaccinated animals, in form of swelling areas not exceeding 2 cm of diameter, 4 days after the second injection. The swellings disappeared in 6 days.

In conclusion, the safety of repeated administration of one dose of the vaccine has been shown based on the results of the study above. A transient increase in temperature and limited local reactions were observed and are adequately addressed in the SPC.

Examination of reproductive performance

No study has been carried out to assess the safety in pregnant or lactating sows, or in breeding boars. Therefore Suvaxyn Circo cannot be recommended for use in these categories of the target species and this has been addressed in the SPC.

Examination of immunological functions

No specific tests on immunological functions were carried out and this is acceptable because the antigens contained in the vaccine, as well as the adjuvant system used are not known to have an impact on immune function.

User safety

A user risk assessment compliant with the CVMP Guideline for user safety for immunological veterinary products (EMEA/CVMP/IWP/54533/2006) was provided. Potential risks were identified.

The active substances of Suvaxyn Circo+MH RTU are inactivated and are not cause of concern to the user.

The excipients used in the vaccine are either authorised food additives in the EU or other substances included in table 1 (allowed substances) of annex to Commission Regulation (EU) No 470/2009 with a no MRL-required status, or included in the list of substances not falling within the scope of Regulation (EC) No 470/2009.

The adjuvant is composed of squalane, polysorbate 80 and poloxamer 401. The last two mentioned substances are known to trigger anaphylactic type reaction. However, it is reasonable to conclude that the risk of anaphylactic type reactions after parental exposure to the user would be minimal.

Risks are essentially associated with handling and accidental self-injection. Exposure to vaccine is limited to the 2 ml volume of a vaccine dose.

The vaccine does not contain any mineral oil material. In safety studies in piglets, the vaccine was well tolerated at the injection site and the product is sterile which decreases the risk of infection upon self-injection.

Consequently, the risk is considered to be minimal and no specific warning has been included in the SPC.

Study of residues

The active ingredients being substances of biological origin intended to produce active immunity, do not fall within the scope of Regulation (EC) No 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin thus no residue studies are required.

The excipients, including adjuvants, are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no maximum residue limits (MRLs) are required, or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

The gentamicin used in cell culture is present at low residual levels in the finish medicinal product. The expected levels of gentamicin at injection site are more than 100 times below the porcine muscle MRL.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

No data concerning interactions with other veterinary medicines were provided and the respective standard warnings are stated in the SPC.

Field studies

Seven (7) field studies were performed with the aim to evaluate the safety of Suvaxyn Circo+MH RTU in 3 week old commercial piglets. Four (4) studies reported to be GCP-compliant were conducted in Europe one (1) study was a multisite study conducted in US (3 different sites) and 2 in Thailand. The non-EU studies can only be considered as supportive information as epidemiological and farm practicing conditions are different.

A field trial was conducted in a commercial farm in The Netherlands to evaluate both safety and efficacy of Suvaxyn Circo+MH RTU. A total of 130 piglets were enrolled. A group of 65 animals were administered by IM a dose of vaccine at medium potency (PCV2 of 3.4 RP of and *M. hyopneumoniae* of 2.4 RP) and a group of 65 animals was used as control group and treaded with saline solution. General signs of safety were monitored by close surveillance during the first hour after vaccination, temperature measurement within 4 hours and weight gain was recorded over a 1-month period after vaccination. Local reactions were monitored until disappearance. Besides, animals receiving individual antibiotic treatment, health events and mortality over the 30-day period were monitored as well. No signs of anaphylactic reaction were observed after vaccination. The average rectal temperature was significantly increased 4 hours post vaccination (average increase 0.6 °C) in the vaccine group when compared to the control group, and returning to normal the day after. Swelling at the injection site was observed in 13% (2 out of 13) of the vaccinated animals one day post vaccination, with a diameter not exceeding 0.5 cm and disappearing within two days. No redness, pain or heat at the injection site was observed at any time point. Body weights between treatment groups did not differ significantly during the trial. Any other health event observed during the study was not related to the product.

It can be concluded that the study demonstrated that a single dose of the Suvaxyn Circo+MH RTU was safe when administered by IM to approximately 3-week old piglets under field conditions.

A second field trial was conducted in a commercial farm in The Netherlands to evaluate both safety and efficacy of Suvaxyn Circo+MH RTU. A total of 399 21-day old piglets were enrolled in this study. A group of 200 animals were administered by IM a dose of vaccine at below minimum release potency (PCV2 of 1.46 RP and *M. hyopneumoniae* of 1.16 RP). This is considered acceptable because the design of this study was done to assess also the efficacy of the product. A group of 199 animals was used as control group and treated with saline. General signs of safety were monitored around vaccination, and weight gain was monitored the day before vaccination, at the transfer to the fattening stable and at slaughter. No anaphylaxis-like symptoms were observed after vaccination in the vaccine. Body weights between treatment groups did not differ significantly.

In conclusion, this study also demonstrated that it have been demonstrated that a single dose of the Suvaxyn Circo+MH RTU was safe when administered by IM to approximately 3-week old piglets under field conditions.

A third field trial was conducted in a commercial farm in The Netherlands to evaluate both safety and efficacy of Suvaxyn Circo+MH RTU. A total of 130 piglets were enrolled in this study. A group of 65 animals were administered a dose of vaccine at medium potency (PCV2 of 3.4 RP and *M. hyopneumoniae* of 2.4 RP) and a group of 65 animals was used as control group and treated with saline solution. General signs of safety were monitored by close surveillance the first hour after vaccination,

temperature measurement from the day before until 4 days after vaccination and by weight gain over a 1 month period after vaccination. Local reactions were monitored until disappearance. Besides antibiotic treatment, health events and mortality over the 30-day period were monitored as well. No anaphylaxis-like symptoms were observed after vaccination, in neither the vaccine nor the control group. The average rectal temperature was significantly increased 4 hours post vaccination (average increase 1.0 °C) in the vaccine group when compared to the control group. That difference was no longer present one day post vaccination. No swelling, redness, pain or heat at the injection site was observed at any time point. Body weights between treatment groups did not differ significantly just prior to vaccination and 14 days thereafter. Any other health event observed during the study was not related to the product.

In conclusion, this study demonstrated that a single dose of the Suvaxyn Circo+MH RTU was safe when administered under field conditions.

The fourth field trial was conducted in a commercial farm in the United Kingdom to evaluate the safety of Suvaxyn Circo+MH RTU. A total of 130 piglets were enrolled in this study. A group of 65 animals were administered a dose of vaccine at medium potency (PCV2 of 5.92 RP and *M. hyopneumoniae* of 2.92 RP) and a group of 65 animals was used as control group and traded with saline solution. General safety signs were monitored by close surveillance during the first hour after vaccination. The temperature was measured from the day before vaccination until 4 days post vaccination and weight gain was monitored for 1 month post vaccination. Local reactions were observed until disappearance. Besides antibiotic treatment, health events and mortality for 30 days were monitored. No anaphylaxis-like symptoms were observed after vaccination, in neither the vaccine nor the control group. The average rectal temperature was not significantly different at any time point measured. Four (4) hours post vaccination the average increase was 0.4 °C in the vaccinated group when compared to the control group. Swelling at the injection site was observed in 20% (3 out of 15) of the animals in the vaccinated group one day post vaccination, with a diameter not exceeding 0.5 cm. Two (2) days after vaccination, these swellings were no longer detected. No redness, pain or heat at the injection site attributable to the candidate vaccine was observed at any time point. Body weights between treatment groups did not differ significantly at D1 and after one month post administration. Any other health event observed during the study was not related to the product. No mortality was observed in the study.

In conclusion, this study demonstrated that a single dose of the Suvaxyn Circo+MH RTU was safe when administered by IM to 3-week old piglets under field conditions.

A fifth field study provided was conducted 3 farms located in 3 different states in the US, with the aim of evaluating the safety of Suvaxyn Circo+MH RTU. Three (3) groups of piglets were reared in each farm. In total, 474 pigs were enrolled in the study. Three hundred sixteen (316) pigs were vaccinated with one of 2 batches below the maximum recommended potency (PCV2 RP of 3.4 and *M. hyopneumoniae* RP of 2.4 or PCV2 RP of 3.9, and *M. hyopneumoniae* RP of 2.2). A hundred fifty eight (158) pigs were left unvaccinated as controls and where administer with saline solution. In 2 farms weaned piglets were vaccinated respectively at 16-25 days of age and in the third farm 17-21-day old animals were vaccinated one day before weaning. Clinical signs were recorded for all animals 1 hour and 6 hours post vaccination and on days 1, 7, 13 or 14, and 21 post vaccinations. Injection site observations were performed in all animals 1 and 7 days post vaccination. Animals which developed local reactions after vaccination were monitored daily until resolution of the reaction. Piglets were exposed to natural infectious agent (PRRS or bacteria). The number of vaccinated piglets reporting diarrhoea or respiratory impairment was not statistically different between vaccinated and controls. Mild and transitory local reactions were reported in 1% of piglets (4 out of 316). In conclusion, the safety evaluation of the vaccine was favourable. Results however were only supportive.

In two studies that were conducted in Thailand, in the same farm with piglets at different ages 3 or 5-6 weeks. They were vaccinated with 4 batches of Suvaxyn Circo+MH RTU (3.0 to 3.6 PCV2 RP and 2.25 to 3.45 *M. hyopneumoniae* RP). Unfortunately the studies were inconclusive because digestive disorders occurred both in vaccinates and controls over the monitoring period.

Nevertheless, as the study was conducted outside EU and also the vaccine used was produced locally, results from this field study can only be considered as supportive.

Environmental risk assessment

A risk assessment has been provided in compliance with the CVMP Guideline on the environmental risk assessment of immunological veterinary medicinal products (EMEA/CVMP/074/95).

Hazard identification

The two vaccine strains included in the product are inactivated. The adjuvant is constituted by a mixture of squalane and non-ionic surfactants which are included in the list of compound for which no MRL is required. Thiomersal ($C_9H_9HgNaO_2S$), mercury containing organic compound is the most toxic for the environment.

Exposure to hazard

Since the product is used in piglets and administered by IM, direct exposure of the environment does not occur. Any unused product or waste should nevertheless be disposed of by the appropriate channels. The only toxic component that would be excreted by vaccinated pig is the mercury from the thiomersal. A maximum of 12.5 mg of mercury could be released in the environment if a bottle is spilled which would be dispersed by water and will not reach significant concentrations in the environment.

Based on the data provided the ERA can stop at phase I. Suvaxyn Circo is expected to pose a negligible risk for the environment when used according to the SPC.

Environmental risk assessment for products containing or consisting of genetically modified organisms

Not applicable.

Overall conclusions on the safety documentation

The safety of Suvaxyn Circo+MH RTU in target species was investigated in five (5) laboratory safety studies reported to be GLP-compliant, performed in accordance with Ph. Eur. monograph 0062 on Vaccines for veterinary use and Ph. Eur. monograph 5.2.6 on Evaluation of safety of veterinary vaccines and immunosera. This was acceptable as Suvaxyn Circo+MH RTU has been centrally authorised for the target species and contains PCV2 as the applicant product.

Three (3) GCP-compliant field safety and efficacy studies and 1 GCP-compliant field safety studies were also provided. Three (3) more field studies were provided however as they were conducted in US and Thailand, results can only be considered as supportive.

Results from laboratory studies demonstrated the safety of a single dose administration and of a 2-fold overdose administration of Suvaxyn Circo+MH RTU. In addition, the safety of repeated administration of one dose of the vaccine has been shown.

Transient hyperthermia up to 1 °C after vaccination was very commonly reported. Increase in temperature of 2 °C was also commonly reported. Since the hyperthermia shown in the field trials was higher than in laboratory studies, where the vaccines administered contained a higher amount of antigens, it may be concluded that adjuvant would rather be the cause of such increase in temperature.

Immediate mild hypersensitivity-like reactions may occur uncommonly after vaccination and anaphylaxis may occur in very rare cases. In case of such reactions, appropriate treatment is recommended.

Local tissue reactions in the form of swelling below 2 cm in diameter, which may be associated with local heat, redness and pain at palpation, were observed commonly at the injection site, due to mild inflammatory response. The local tissue reactions disappeared within 2 days. The adverse reactions drawn from Suvaxyn Circo+MH RTU data may be extrapolated to Suvaxyn Circo are appropriately reflected in its SPC.

The potential effect on reproductive performance was not investigated on the basis that the vaccine is not intended for breeding animals and this is considered acceptable.

Residue studies are not required. The withdrawal period is set at zero days.

The user safety has been adequately addressed. The user safety for this product is acceptable when used as recommended in the SPC.

Suvaxyn Circo is expected to pose a negligible risk to the environment when used according to the SPC.

Based on Suvaxyn Circo+MH RTU data, Suvaxyn Circo is considered safe when used as recommended in the SPC.

Part 4 – Efficacy

Introduction and general requirements

PCV2 is a virus involved in a large array of syndromes which has been recently classified (Segalés, 2012) in the 6 main following groups: PCV2 subclinical infection (PCV2-SI), PCV2 systemic disease (PCV2-SD), PCV2 lung disease (PCV2-LD), PCV2 enteric disease (PCV2-ED), PCV2 reproductive disease (PCV2-RD), Porcine dermatitis and nephropathy syndrome (PDNS).

A correlation has been demonstrated between the amount of PCV2 virus and the severity of disease (Grau-Roma et al., 2009).

The diagnosis of the diseases relies on the presence of clinical signs associated with the PCV2 load and typical histopathologic changes of the target tissues (Sorden’s criteria).

Vaccination is expected to reduce viral load in blood and lymphoid tissues and virus faecal shedding caused by infection with PCV2.

The efficacy of Suvaxyn Circo+MH RTU was investigated in seven (7) laboratory studies compliant to the Ph. Eur. monograph 0062 on Vaccines for veterinary use and Ph. Eur. monograph 5.2.7 on Evaluation of efficacy of veterinary vaccines and in four (4) field studies reported to be GCP compliant. This was acceptable as Suvaxyn Circo+MH RTU has been centrally authorised for the target species and contains PCV2 as the applicant product.

In laboratory studies, piglets of minimum age (3 weeks) were challenged by a PCV2a strain with the aim to detect the onset of immunity (OOI) and by a PCV2b strain with the aim to detect the duration of immunity (DOI) as well as the interference with maternally derived antibodies (MDA). Since cross protection is described in literature against PCV2b and PCV2a, the changing of challenge strains is acceptable. The route of administration of the challenge was changed over the studies and this is acceptable. As further described below, challenges were carried out whether 1 time by intranasal route (IN) or 2 times by IM and IN route.

In the laboratory studies, clinical and biological parameters including viral load or excretion, lesions and immune response were monitored by validated tests (qPCR), histology lesions, serology and immunohistochemistry). In field studies zoo-technical parameters such as antibiotic consumption, mortality, and weight gain were also monitored.

Challenge model: the challenge model is the one required by the Ph. Eur. monograph 0062.

Laboratory trials

Onset of immunity

Two (2) laboratory studies were performed with the aim to establish the OOI of the PCV2 part of Suvaxyn Circo+MH RTU. Animals enrolled in these studies were tested to be PCV2 antibody free and PCV2 DNA free in the serum before vaccination.

In the first study provided a total of 120 3-week old pigs were enrolled. Four (4) groups of 24 pigs each were treated with vaccines containing different amounts of PCV2 antigens below the minimum potency proposed (RP from 0.22 to 2) by IM, one group of 24 pigs was used as control group and vaccinated with a product containing only the *M. hyopneumoniae* antigen at high potency (RP of 1.71) by IM. Piglets were challenged at 6 weeks with PCV2a virulent strain (10^5 FAID50/ml (fluorescent antibody infectious dose)) by 2 different administration routes: 1 ml IM and 2 ml IN. Animals were observed for clinical signs for 3 weeks after challenge and sacrificed at day 45. After vaccination a total of 4 pigs (distributed in 3 groups of 24 vaccinated animals) expressed signs of anaphylactic type reactions such as vomiting, diarrhoea or depression and erythema. The challenge caused also frequent mild anaphylactic-type reactions. One week after challenge, the viraemia was lower in the vaccinated group than in the control group (by a mean of 10^4 copies genome of PCV2a) and was always undetectable for at least 60% of them. The virus faecal shedding was decreasing in the same percentage of animals during the 2nd and 3rd week after challenge (around 1 DNA copy instead of 20,000 DNA copies in control animals).

During the study, 5 piglets were found viremic before D21, confirming that PCV2 natural infection circulated before challenge, however the study is acceptable since the validity criteria set by the applicant were met as only less than 10% of pigs were PCV2 positive (by real-time PCR) and the mean PCV2 antibody titre in the control group remained negative until challenge.

The second study provided presented with a similar study design to the previous study (24 pigs allocated in 4 groups vaccinated with different amount of PCV2 antigen and in 1 control group), the same batches of vaccines and a similar challenge (final titre of 10^5 FAID50/ml). Thirty nine (39) out of 96 vaccinated animals presented signs of anaphylactic reaction after challenge. Results showed that 1 week after challenge viraemia was decreased by about 10^3 genome copies in 50% of the vaccinated pigs and the other 50% did not show any viraemia. Virus shedding was reduced in each vaccinated group regarding both the quantity of the virus excreted (by about 10^3 genome copies) and the percentage of pigs shedding the virus (25% to 43%) when compared to the percentage of control pigs (83% were

shedding the virus). Moreover, the percentage of animals with respectively lymphocytic depletion and histiocytic replacement in the lymphoid organs were decreased in all vaccinated groups from 48% to 4-12% and from 39% to 4-8% when compared to the control group. In the group of pigs treated with the vaccine at the highest potency no histiocytic lesions were detected. The virus load in tonsils was also significantly decreased in all the vaccinated groups.

A PCV2 natural infection was detected in one vaccinated pig 1 week before challenge, however the study was considered acceptable due to absence of seroconversion in the control group from the same pen.

A complementary study was performed in US where Suvaxyn Circo+MH RTU with 2 different vaccination schedules were compared with 2 competitors. Conventional piglets (48 animals per group) were vaccinated at the age of 3 weeks with a commercial batch (PCV2 RP = 4.7) and thus were given a dual challenge (PCV2 65 days after vaccination + *M. hyopneumoniae*, 51 days after vaccination).

Significant reduction of PCV2 viral load in blood, of faecal shedding, of viral load in lymphoid tissues and average daily weight gain were shown for the vaccinated groups. Piglets administered with 2 injections were less frequently PCV2 viremic than those with 1 injection (8.3 & 8.7 vs 27.7 & 10.4). However, this difference is not corroborated by PCV2 shedding, microscopic lesions of lymphoid organs, the average weight gain.

In conclusion, based on the results of the above studies, and in particular results from the first two studies regarding the reduction of PCV2 viremia and PCV2 virus shedding as well as the reduction of lesions and virus load in lymphoid tissues in 1 study the claimed as OOI at 3 weeks after vaccination was supported . These indications were corroborated by another study carried out with a commercial batch (RP higher than the minimum threshold).

Duration of immunity study

One (1) laboratory study was provided with the aim to establish the DOI at 23 weeks post vaccination A total of 60 crossbred piglets were enrolled in this study. Thirty (30) crossbred piglets were treated at 3 weeks of age with 4 ml of vaccine below the minimum of potency (RP of 1.03) by IM route and 30 pigs were used as controls (treated with a placebo). Twenty three (23) weeks later, animals were challenged by IN administration with 4 ml of a PCV2b strain containing a titre of $10^{5.7}$ TCID50/ml. No signs of anaphylactic shocks were recorded post vaccination. In the vaccinated group, viremia was prevented in 100% of the pigs and the number of pigs shedding the virus was significantly reduced in the vaccinated pigs (20.7%) compared to the control group (60.7%). The number of pigs presenting lymphocyte depletion and histiocytic replacement in the lymphoid organs was similar (about 10%) in both vaccinated pigs and controls, however detection of PCV2b load in the lymphoid organs was lower in vaccinated pigs and this difference was statistically significant. Results showed that vaccinated and control pigs had a similar growth rate.

In conclusion, the DOI for PCV2 was demonstrated in this study at 23 weeks post vaccination, on the basis of reduction of PCV2 viremia, PCV2 shedding and viral load in lymphoid organs.

Interference study

In one laboratory study, the interference between *M. hyopneumoniae* antigens on the potency of PCV2 antigens was investigated. In this respect, 120 3 -week old piglets were vaccinated with different batches of vaccines incorporated various amount of *M. hyopneumoniae* antigens with a same amount of PCV2 antigen below the lowest RP of a commercial batch (0.9 RP). The amount of *M. hyopneumoniae*

antigens ranged from 0 to 2 RP which was far below the maximum amount of 3.8 RP. Animals were PCV2a challenged 3 weeks after vaccination and necropsied 21 days after challenge.

Piglets remained PCV-free until challenge (PCV neither in blood nor in faeces). Challenge actually induced lesion in control animals, confirming its validity.

Vaccinates had lower viremia and shedding than control over the 5 sampling time points after challenge as well as lesser lymphoid lesions within lower PCV2a.

The presence or absence of *M hyopneumoniae* antigen content in the vaccine did not modify the PCV2 viremia (% of animal ever viremic as well as the intensity of viremia) and the PCV2a load of lymphoid organs.

No conspicuous evidence of interference was thus detected. Therefore efficacy data obtained with Suvaxyn Circo+MH RTU may be extrapolated to Suvaxyn Circo in compliance with guideline EMA/CVMP/IWP/594618/2010.

Interference of maternal antibodies

Two (2) laboratory studies were provided with the aim to evaluate the potential interference of MDA.

In the first study provided, sixty (60) 3-week old MDA-positive (MDA+) piglets, (1.1-1.2 S/P ELISA) were enrolled. Thirty (30) piglets were administered a vaccine containing the PCV2 antigen below the minimum of potency (RP of 0.97) and *M. hyopneumoniae* at high potency (RP of 2.03) by IM route, and 30 piglets were used as controls and treated by IM only with a product containing only *M. hyopneumoniae* antigen at high potency.

The animals were challenged 5 weeks after vaccination with a PCV2b virulent strain which was administered by IN (2ml) and by IM (1ml). Three (3) piglets out of 60 showed signs of anaphylactic reaction. After challenge, PCV2 antibodies increased significantly in the vaccinated group compared to the control group. Vaccination did not significantly decrease the viremia and faecal shedding when piglets had MDA. This study was considered invalid by the applicant due to the presence of MDA level during the challenge that interfered with the PCV2 viremia (only 31% of the controls were PCV2 viremic). However, results after the challenge (% of viremic and % of pigs shedding the virus) in control pigs were similar to those presented in the following study.

Due to the high antibody levels in all groups of pigs, the protective potential of the vaccine might have been masked and conclusion could not be drawn.

In the second study provided, the interference of MDA was investigated in 23 to 27-day old pigs with a lower level of MDA during the challenge (0.15 S/P ELISA) than in the first study. The level of MDA was also lower at the time of vaccination (0.74 S/P ELISA). A total of 96 pigs (approximately 3 week old) were enrolled in this study. Two (2) groups of 24 pigs each were treated by IM with different vaccines containing intermediate potency (PCV2 RP of 1.01) and high potency (PCV2 RP of 2.33) of the final formulation. One group of 24 MDA-negative (MDA-) pigs was treated with the vaccine at intermediate strength (PCV2 RP of 1.01) but due to the study design and study conditions, statistical comparison with other groups was not relevant because of not forming part of the same randomization process and results from this group could not be taken into account. One (1) group of MDA+ pigs was used as a control group and treated with a placebo by IM.

All 4 groups, were challenged 35 days after vaccination by administration of PCV2b strains (about 10^6 TCID50) by both IN and IM routes. The challenge was not strong enough to cause pathological lesions but 52% of the MDA+ control group showed viremia. No MDA- unvaccinated control group was included

in the study to compare the MDA interference on viremia and virus shedding after challenge. The vaccine with intermediate potency (PCV2 RP of 1.01) was not efficient enough to decrease viremia, virus shedding and virus load in tracheobronchial, mesenteric and inguinal lymph nodes as well as in tonsil of MDA- animals. However, MDA+ pigs with a level of MDA at vaccination about 0.7 S/P ELISA, when administered with the vaccine at minimum release potency (PCV2 RP 2.33) showed a decrease in viremia, viral load in lymphoid organs and in faeces when compared to MDA+ control group.

In conclusion, while interference cannot be ruled out, the indications were met in presence of MDA in the second study since a statistically significant decrease in viremia, viral load in lymphoid organs and faecal shedding was demonstrated after the challenge, in animals vaccinated with PCV2 vaccine at minimum release potency (RP of 2.33) in presence of MDA levels representative of field conditions at vaccination. Therefore no specific warning in the SPC is necessary.

Field trials

Three (3) field studies reported to be GCP-compliant by the applicant were conducted in 3 commercial pig farms in The Netherlands with the aim to evaluate the efficacy of Suvaxyn Circo+MH RTU.

In the first field study provided a total of 130 conventional 21-day old piglets were enrolled. Circulation of PCV2 and *M. hyopneumoniae* was confirmed by serology before vaccination. One group of 65 pigs was treated with an intermediate potent vaccine (PCV2 RP of 3.4 and *M. hyopneumoniae* RP of 2.4) and one group of 65 piglets was left as control and administered with saline solution. No PCV2 or *M. hyopneumoniae* seroconversion was observed after vaccination. A natural infection with PCV2 occurred after day 118 of the study. This was confirmed by the occurrence of PCV2 viremia and faecal shedding in the control group as well as seroconversion in both the control and the vaccinated group. PCV2 viremia was significantly lower in the vaccinated group.

No difference in PCV2 shedding, lung lesions, mortality and percentage of animals receiving an antibiotic treatment during the study period was observed between vaccinates and controls. Growth was similar until day 89, thus before the PCV2 natural infection was detected, between the groups. At the end of the observation period (day 165), vaccinated pigs showed an average of 4.4 kg of weight gain compared to controls. Lung lesion scores at slaughter were low. The difference was not statistically significant.

Results from this study showed that Suvaxyn Circo+MH RTU were able to significantly reduce PCV2 viremia but not to reduce *M. hyopneumoniae* associated lung lesions.

In the second field study provided, 399 conventional pigs 19-24 day of age were enrolled. Two hundred (200) piglets were vaccinated by IM with a low potency vaccine (PCV2 RP of 1.42 and *M. hyopneumoniae* RP of 1.16), further 200 piglets were kept as controls and administered saline solution. The finishing farm presented a history of PCV systemic disease and natural circulation of PCV2 happened between day 89 and 119.

Results from vaccinated pigs showed decreased PCV2 viraemia-not statistically significant- compared to the control group but not lower PCV2 faecal shedding. Zoo-technical parameters, such as growth and mortality, were similar despite the antimicrobial treatment in both groups.

The third field study provided, a total of 130 19 to 23-day old piglets were enrolled. A group of 65 piglets were vaccinated with high potency (PCV2 RP of 3.4 and *M. hyopneumoniae* RP of 2.4) and a group of 65 piglets was left unvaccinated as control and injected with saline solution. The farm reported a history of *M. hyopneumoniae* lesions at slaughter however, during the field study no *M. hyopneumoniae* infection circulated. On the other hand, circulation of PCV2 was detected

serologically and viraemia rose from the start of the study.

Results from vaccinated piglets showed statistically significant decreased in viraemia during PCV2 infections; however, no reduction in shedding or clinical and zoo-technical parameters (such as increased weight gain, mortality) was shown.

Conclusion from EU field studies

PCV2 infections occurred in each field studies at different time. Field studies demonstrated that vaccine is efficacious in decreasing PCV2 viraemia regardless of the potency of the vaccine. Lesions and PCV2 load in the lymphoid organs were not investigated in the field studies. Only few animals died during the studies, and there was no difference between the percentages of piglets with PCV2 positive lesions. Regarding to the clinical efficacy, the impact on the growth was not clinically relevant; the weight gain was statistically significantly improved only when the PCV2 infection was present at a late stage of the life cycle (about 1 week before slaughtering). In fact, no positive impact on weight gain was shown when the PCV2 natural infection occurred in earlier stage of the life, i.e. 9 weeks before slaughter or 13 weeks before slaughter. Furthermore, vaccination did not decrease PCV2 faecal shedding. In conclusion, the 3 field trials supported only the decrease of a PCV2 viraemia.

Data from four studies conducted in the USA were presented and were considered supportive of this dossier.

In study, the clinical efficacy of Suvaxyn Circo+MH RTU was compared to a placebo and 3 other commercial vaccines according to manufacturers' label recommendations. Clinical parameters and economic performance of pigs challenged with *M. hyopneumoniae* and porcine circovirus type 2 (PCV2b) were evaluated in this study. Four hundred eighty (480) high-health status pigs from a US high health status herd that is PRRS and *M. hyopneumonia*e stable, were randomly allocated to one of six treatment groups, and vaccinated IM. All pigs were challenged with *M. hyopneumonia*e and PCV2b, 2 and 4 weeks after the second vaccination, respectively. A subset of pigs from each treatment was randomly allocated to be necropsied either 2 or 4 weeks after PCV2 challenge. These pigs were evaluated for post-challenge clinical signs, PCV2 viraemia, and macroscopic and microscopic lesions at necropsy. The remaining pigs were retained for 173 days, or until the average weight is approximately 285 pounds. At periodic time-points serum samples were taken for serological evaluation and pigs were weighed for calculation of average daily gain.

PCV2-associated disease (PCVAD) fatalities occurred, all in the control group.

Whatever the vaccination, vaccinates had lower PCV2 viraemia, their average daily gain (ADG) on day 146 was significantly greater (≥ 1.60 lbs vs. 1.56 lbs; $P < 0.05$). And compared to groups given two PCV2 vaccine doses (T3 and T5 groups), Suvaxyn Circo+MH RTU had significantly lower least squares mean (LSM) PCV2 serologic responses and significantly higher levels of post-challenge (PC) PCV2b viraemia and faecal shedding as determined by qPCR assay.

Two other field studies combined with a laboratory challenge were carried out in the USA to support the registration of Suvaxyn Circo+MH RTU in the Association of Southeast Asian Nations (ASEAN) region.

In the field trial a total of 120 3 week old piglets were enrolled. Groups of 30 animals were administered by IM a dose of 1 of the 3 commercial lots of the vaccine at medium potency (PCV2 of 3.4 to 4.7 RP of and *M. hyopneumoniae* of 2.25 to 2.45 RP) or a saline solution (control group). One week prior to challenge they were moved into a facility. They were challenged by a PCV2a strain, 6 weeks after vaccination (Day 42) and necropsied on Day 63. Six pigs of an environmental control group were necropsied on Day 40 prior to challenge.

Piglets were infected by PCV2 prior to challenge; viraemia was detected by qPCR in all groups (1 piglet from the environmental group; half of the control group) as well as shedding in one third of the faeces. But no pathological impact of this natural infection was substantiated in the lymph nodes from the environmental control group.

Vaccination with 3 batches led to a reduction of the viral load in the blood, in the lymphoid tissues and in the faecal shedding by comparison with controls 20 days after the challenge. However, although the percentage of viremic piglets decreased from 96% down to 57-72%, the percentage of faecal shedders was about 100% in all groups.

In the field study carried on concomitantly to the previous one and with the same design except that the pigs were challenged 23 weeks after vaccination at the end of the proposed DOI, with commercial vaccine batches different from those used in the previous study. Piglets were infected by PCV2 prior to challenge as well. However, conversely to the previous study where the vaccination had no impact on PCV2 shedding, the percentage of infected animals was decreased by vaccination since both viremic and shedding animals were lower in the vaccinated groups. Finally, the reduction of the viral load in the blood, in the lymphoid tissues and in the faecal shedding was confirmed in the vaccinates 23 weeks after vaccination.

Overall conclusion on efficacy

The proposed claims that the vaccine reduces viral load in blood caused by infection with PCV2 from 3 weeks after vaccination have been satisfactorily supported by laboratory and field studies. The reduction of viral load in lymphoid tissues and faecal shedding were supported by laboratory studies only. All efficacy studies were conducted with a similar product already approved in the EU, containing PCV2 and *Mycoplasma hyopneumonia* (Suvaxyn Circo+MH RTU). No evidence of interference between *M. hyopneumonia* antigens on the potency of PCV2 antigens was found during relevant investigations. Therefore efficacy data obtained with Suvaxyn Circo+MH RTU can be extrapolated to Suvaxyn Circo in compliance with the guideline EMA/CVMP/IWP/594618/2010.

The OOI was demonstrated in 6-week old piglets, 3 weeks after vaccination.

The DOI was demonstrated at 23 weeks post vaccination.

In presence of MDA representative of field conditions, the vaccine met the claims of reduction of viraemia, viral load in lymphoid organs and virus faecal shedding.

Part 5 – Benefit-risk assessment

Introduction

Suvaxyn Circo is an inactivated vaccine intended for active immunisation of pigs from 3 weeks against PCV2 to reduce viral load in blood and lymphoid tissues and faecal shedding caused by infection with PCV2. Suvaxyn Circo is a monovalent vaccine derived from the bivalent vaccine Suvaxyn Circo+MH RTU, and contains an inactivated recombinant chimeric porcine circovirus type 1 containing the porcine circovirus type 2 ORF2 protein.

The application has been submitted in accordance Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

In well-conducted laboratory studies the vaccine was shown to induce active immunisation of pigs against PCV2 in order to reduce viral load in blood and lymphoid tissues and faecal shedding caused by infection with PCV2. The product was shown to have an OOI at 3 weeks after vaccination with DOI of 23 weeks after vaccination against PCV2.

The efficacy of the vaccine was adequately confirmed in the presence of MDA.

Additional benefits

None identified.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out in general indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

For the target animals

Administration of Suvaxyn Circo in accordance with SPC recommendations is generally well tolerated in the target animal. In laboratory and field studies a transient increase in rectal temperature was frequently observed. Local reactions of maximum 2 cm in diameter were observed which disappeared within 2 days after vaccination. The vaccination did not negatively impact the daily weight gain until the end of the observation period. Immediate mild hypersensitivity-like reactions, resulting in transient clinical signs such as vomiting, diarrhoea or depression, may occur uncommonly after vaccination and this is adequately reflected in the SPC. Anaphylaxis may occur in very rare cases. In case of such reactions, appropriate treatment is recommended.

For the user

The CVMP concluded that the user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment

The product is not expected to pose a risk to the environment when used according to SPC.

For the consumer

The withdrawal period is set at zero days.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user, consumer, and the environment and to provide advice on how to

prevent or reduce these risks.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for active immunisation of pigs from 3 weeks against PCV2 to reduce viral load in blood and lymphoid tissues and faecal shedding caused by infection with PCV2.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the general conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures, including withdrawal period have been included in the SPC and other product information.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Suvaxyn Circo is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).