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"DECENTRALISED" PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

PERSOVAC

23/12/2019

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0366/001/DC
Name, strength and pharmaceutical form	Persovac lyophilisate and solvent for suspension for injection
Applicant	Ceva Phylaxia Veterinary Biologicals Szallas Utca 5 1107 Budapest Hungary
Active substance(s)	Live PRRS virus strain P120
ATC Vetcode	QI09AD03
Target species	Pigs (for fattening)
Indication for use	Active immunisation of pigs from 3 weeks of age in a contaminated PRRS virus environment to reduce viraemia associated with European PRRS virus strains (genotype 1) infection OOI: 3 weeks post vaccination DOI: 24 weeks post vaccination

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/ (in French)

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	18/12/2019
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, HR, HU, IE, IT, LT, LV, NL, PL, PT, RO, SI, SK, UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC, in particular regarding boars and seronegative pregnant animals.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains live porcine reproductive and respiratory syndrome (PRRS) virus strain P120, 4.0 to 7.3 log10 CCID50/dose.

The excipients are casein hydrolysate, mannitol, povidone, sucrose, potassium dihydrogen phosphate, dipotassium phosphate, potassium glutamate monohydrate, bovine serum albumin fraction V.

The container/closure system consists of glass vial, with bromobutyl closure and aluminium cap for the lyophilisate, and polypropylene bottle with polypropylene stopper and aluminium cap or in low density polyethylene bottle, with bromobutyl stopper and aluminium cap for the solvent Vaccesol. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strain and formulation are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

Starting materials of non-biological origin used in production comply with relevant pharmacopoeia monographs where these exist, or in-house specifications.

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

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. <Control on intermediate products> (pharmaceuticals) <Control tests during production> (immunologicals)

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular for the lyophilisate: appearance, identification and titration of the active ingredient, sterility, test for mycoplasma and residual moisture; and for the solvent: appearance, extractable volume, sterility.

The demonstration of the batch to batch consistency is based on the results of 4 batches of lyophilisate and 5 batches of solvent produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

Stability data on the active substance have been provided, demonstrating the stability of the active substances when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (1 year for the lyophilisate, 3 years for the solvent Vaccesol) when stored under the approved conditions (at 2-8° C for the lyophilisate, below 25°C for the solvent).

The in-use shelf-life of the reconstituted vaccine (6 hours) is supported by the data provided (pH and titre stable).

III. SAFETY ASSESSMENT

The vaccine batches used were manufactured according to part II.

Laboratory trials

The safety of the administration of one dose and an overdose in the target animal is demonstrated in 2 studies. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.
Each of the two studies involved equal numbers of vaccinated and control SPF piglets of the minimum age, vaccinated by IM route.
The 30 piglets of the dose study were observed 14 days after vaccination for local and general clinical signs, and for post-mortem examination of lungs, spleen, tonsils and injection site when euthanised on day 14.
The 20 piglets of the overdose study were observed 21 days after vaccination for local and general clinical signs, and for post-mortem examination of lungs, tonsils, mediastinal lymph nodes and injection site when euthanised on day 21.

The effects observed and their frequency were reported in the SPC.

The safety of the repeated administration of one dose was not investigated, as Persovac is intended for single use only.

Effects on reproductive performance were examined. Results difficult to interprete were obtained in pregnant seronegative gilts vaccinated with passaged and unpassaged vaccine strain; thereafter a specific study was performed and confirmed safety in seropositive gilts. Vaccination/ exposure of seronegative sows and gilts should be avoided because of potential adverse effects on reproductive performances. Vaccination of boars is contraindicated due to the dissemination of the vaccine virus (see below). This information is reported in the SPC.

Specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strain. Information was provided regarding the genome sequences of the vaccine strain. The vaccine strain disseminates in the body and remains detectable in tonsils for months, and can spread at low rate to animals in contact. After artificial passages in animals, when administered to piglets, the viremia induced by the passaged strain was higher than the unpassaged strain but it was not associated with an increase in pathogenicity (clinical signs and lung lesions of piglets). All these observations led to specific warnings in the SPC.

The excipients used are either listed in annex 1 of Commission Regulation (EU) 37/2010 or considered as substances not falling in the scope of regulation (EC) N° 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin. Based on this information, no withdrawal period is proposed.

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

Field studies

2 field studies were performed in 3 different sites. They involved 500 piglets, half of them vaccinated, the other receiving a placebo. There was no significant difference in clinical signs and growth performances. The local reactions were in line with those described in SPC.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

- The immunological active component (viral strain) does only infect pigs and was shown to be safe for the intended category (fattening pigs)
- The vaccine virus might be excreted by vaccinated pigs. However, as the vaccine is only intended for use on farms that already are infected (often by a wild-type pathogenic PRRSv) this is of no consequence.
- Further components incorporated into the vaccine are commonly used in biological products already on the market, they are safe especially taking into consideration the proportions they are present in the vaccine.
- The amount of the vaccine per vaccinated animal is small (1 mL).
- The method of parenteral use of the vaccine ensures that the only product which is not going into the animals will remain in the syringes or in the bottle.
- The vaccination is done by a needle mounted on a syringe.
- The quality of packaging materials complies with the requirements of Ph. Eur.

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

The following information was reported in the SPC:

4.2 Indications for use, specifying the target species

For active immunisation of pigs from 3 weeks of age in a PRRS virus contaminated environment, in order to reduce viraemia associated with European PRRS virus strains (genotype 1) infection. […]

4.3 Contraindications

Do not use in PRRS naïve herds in which the presence of PRRSV has not been established using reliable diagnostic methods.
Do not use in boars producing semen, as PRRS virus can be shed in semen.

4.5 Special precautions for use

Special precautions for use in animals
Care should be taken to avoid the introduction of the vaccine strain into an area where PRRS virus is not already present. The vaccine strain is excreted and thus may infect the susceptible pigs in contacts with vaccinated animals for at least 7 weeks. To avoid this infection, it is advised to vaccinate all target pigs within a herd from the earliest recommended age onwards.
Special precautions should be taken to avoid spreading of the vaccine strain to susceptible (seronegative) pregnant animals (see section 4.7).

4.6 Adverse reactions (frequency and seriousness)

Local reaction below 5 cm in diameter with associated redness is common and resolves spontaneously within 1 day. Upon intramuscular administration slight transient increases (up to 1.1°C) in rectal temperatures occurred very commonly

in the studies. Temperatures return to the normal range without additional treatment, 1 to 3 days after the maximum temperature increase is observed.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Pregnancy:
No information is available on the efficacy in pregnant animals.
The vaccine strain has been shown to be safe in seropositive pregnant animals.
It was shown that the vaccine virus, which is a European field isolate, can cross the placenta in seronegative gilts.
Exposure of the vaccine strain to susceptible (seronegative) gilts/sows should be avoided.

Lactation:
No information is available on the use of the vaccine during lactation period.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

After administration of a 10-fold overdose, no adverse reactions other than those mentioned under adverse reactions were observed.

IV. CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that vaccination is able to reduce viremia following an experimental challenge.
The parameters generally recorded in the laboratory studies were: viral load in sera, weight, clinical signs including mortality, lesions at necropsy. 4 different challenge strains were used, isolated in Spain, Italy, Belgium and France between 1999 and 2013.

The onset of immunity (OOI) was demonstrated by challenges performed 20 or 21 days after vaccination, in 3 studies using 3 different challenge strains and involving each 8 to 10 vaccinates and equal number of control animals of (or close to) the minimum age.
The duration of immunity (DOI) was demonstrated by challenge performed 24 weeks after vaccination, in a study involving 15 vaccinates and 15 control animals of the minimum age.
In an additional study, the nasal excretion was more specifically studied.
The effect of maternally derived antibodies (MDA) was examinated in a specific trial involving 72 piglets, using a challenge.

The following protection was observed:
Significant reduction of viral loads in sera were obtained in vaccinates compared to controls in all the studies.
No significant improvement in weight gain could be demonstrated considering the weight at vaccination and the weight at slaughter, despite sometimes significant improvement of weight gain post challenge could observed.
The data were not sufficient to gain a full claim for reduction in nasal shedding, as this parameter was studied only in a single study in animal not of the minimum age and not challenged at the claimed OOI.
The MDA positive piglets were also protected against the challenge.

Overall, the claims of the SPC are in line with the statistically significant results obtained in these trials.

Field Trials

The applicant has conducted a field study. Because the vaccine strain spreads, biosecurity measures were implemented and this was not compatible with blinding. No claim was based on the results of this field trial.

The following conclusions can be drawn from the results of the studies concerning onset and duration of immunity, indications for use and immunisation scheme:

4.2 Indications for use, specifying the target species

For active immunisation of pigs from 3 weeks of age in a PRRS virus contaminated environment, in order to reduce viraemia associated with European PRRS virus strains (genotype 1) infection.

Onset of immunity: 3 weeks post vaccination
Duration of immunity: 24 weeks post vaccination

In a laboratory trial in seronegative piglets vaccinated at the age of 32 days, a reduction of titre and overall nasal shedding was observed after a challenge 5 weeks after vaccination.

4.9 Amounts to be administered and administration route

For intramuscular administration.
Vaccination of pigs from 3 weeks of age onwards with a single dose of 1 ml.

Reconstitute the vaccine aseptically. Use sterile syringe and needle. Avoid the introduction of contamination during reconstitution and usage.

To reconstitute the vaccine, part of the solvent (Vaccesol) is transferred to the vial containing the freeze dried pellet. After reconstitution of the pellet, the reconstituted material is transferred back to the solvent bottle. Gently shake the solvent bottle to homogenise the vaccine. The vaccine is then ready to use.

V. OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the veterinary Heads of Agencies website (www.HEVRA.org).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.