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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Porcilis Lawsonia lyophilisate and solvent for emulsion for injection for pigs

NO, DK, FI, SE: Porcilis Lawsonia vet

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0357/001/DC
Name, strength and pharmaceutical form	Porcilis Lawsonia Lyophilisate and solvent for emulsion for injection for pigs NO, DK, FI, SE: Porcilis Lawsonia vet
Applicant	Intervet International BV Wim de Körverstraat 35 5831 AN Boxmeer The NETHERLANDS
Active substances	Each dose of 2 ml reconstituted vaccine contains: Active substance (lyophilisate): Inactivated *Lawsonia intracellularis* strain SPAH-08 inactivated $\geq$ 5323 U[1] [1] Antigenic mass units as determined in the in vitro potency test (ELISA).
ATC Vetcode	QI09AB18
Target species	Pigs
Indication for use	For the active immunisation of pigs from 3 weeks of age to reduce diarrhoea, loss of daily weight gain, intestinal lesions, bacterial shedding and mortality caused *by Lawsonia intracellularis* infection.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 32 (3) of Directive 2001/82/EC as amended.
Date of completion of the original procedure	31th July 2019
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden, Spain, United Kingdom

I. SCIENTIFIC OVERVIEW

The vaccine is an inactivated bacteria which is indicated for the immunisation of pigs from three weeks of age and presented in freeze-dried form in a vial to be reconstituted with a vial of solvent presented in liquid form.
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 reactions observed are indicated in the SPC (Summary of Product Characteristics).
The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

Each dose of 2 ml reconstituted vaccine contains:

Active substance (lyophilisate):
Inactivated *Lawsonia intracellularis* strain SPAH-08 ≥ 5323 U[1]
[1] *Antigenic mass units as determined in the in vitro potency test (ELISA).*

Adjuvant (solvent):

Light mineral oil	222.4 mg
Aluminium (as hydroxide)	2.0 mg

The lyophilisate is filled in glass type I containers, closed with halogenobutyl rubber stopper and sealed with an aluminium cap. The solvent is filled in polyethylene terephthalate vials. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains is justified.

The inactivation process and the detection limit of the control of inactivation test are correctly validated.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 practices in a licensed manufacturing site.

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

C. Control of Starting Materials

Starting materials of non-biological origin used in production comply with European 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 ““Guideline on requirements for the production and control of immunological veterinary medicinal products” (EMA/CVMP/IWP/206555/2010-Rev01).

Seed lots and cell banks have been produced 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 tests during production

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

F. Control Tests on the Finished Product

The tests performed on the final product are in line with the relevant requirements; any deviation from these requirements is justified. The tests performed are as follows:

Lyophilisate
- Appearance
- Vacuum
- Solubility
- Potency and identity test
- Endotoxin test
- Sterility: according to Ph. Eur. 2.6.1
- Determination of residual humidity

Solvent
- Appearance
- pH
- Viscosity
- Aluminium content
- Mineral oil content
- Sterility: according to Ph. Eur. 2.6.1

The demonstration of the batch to batch consistency is based on the results of 20 batches of lyophilisate and 8 batches of solvent produced according to the method described in the dossier.

G. Stability

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

The vaccine must be used within 6 hours after reconstitution.

III. SAFETY ASSESSMENT

Laboratory trials

Laboratory safety studies were performed to evaluate the safety of Porcilis Lawsonia alone (15 pigs) or mixed with Porcilis PCV M Hyo (148 pigs). The safety of the intramuscular administration of one dose, an overdose and the repeated administration of one dose in the target species is demonstrated
After vaccinations, no systemic or local reactions related to vaccination were observed in any of the laboratory safety studies. The average temperature increase was in line with Ph.Eur. monograph 2448 (porcine enzootic pneumonia vaccine (inactivated)) requirements in all the laboratory safety studies except in one study in which one pig that received an overdose (cumulative M. hyo potency of 10.86) showed a transient temperature increase to 2.2°C. However, this animal did not show any systemic or local reactions associated with vaccination.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Overall, the vaccine proved to be well tolerated in the target species. The local and systemic reactions observed are described in the SPC (Summary of Product Characteristics) and package leaflet under “adverse reactions”.

The assessment of the interaction of this product with Porcilis PCV M Hyo vaccine was made. The safety and efficacy of this association of vaccines when mixed are demonstrated. Suitable warnings are included in the SPC and package leaflet.

Details are given in the Summary of Product Characteristics (SPC) as follows:

4.6 Adverse reactions (frequency and seriousness)

An increase in body temperature very commonly occurs (mean 0.6°C, in individual pigs up to 1.3°C). The animals return to normal temperature within 1 day after vaccination. Local injection site reactions in the form of swelling (< 5 cm diameter) may commonly occur and disappear within 23 days.

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

The safety of the veterinary medicinal product has not been established during pregnancy or lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Safety and efficacy data are available in pigs from 3 weeks of age onwards which demonstrate that this vaccine can be mixed with Porcilis PCV M Hyo. The product literature of Porcilis PCV M Hyo should be consulted. An increase in body temperature very commonly occurs (mean 1.0°C, in individual pigs up to 2.5°C). The animals return to normal temperature within 1 day after vaccination.

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product except the products mentioned above. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.

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

No adverse reactions other than those mentioned in section 4.6 and the temperature increases described in section 4.8 were observed after the administration of a double dose of Porcilis Lawsonia reconstituted in Porcilis PCV M Hyo.

Field studies

One field safety study was designed for the purpose of collecting safety data of Porcilis Lawsonia mixed with Porcilis PCV M Hyo (102 pigs).
Additionally, safety of vaccines in terms of systemic or local reactions were also collected from four field efficacy studies designed to evaluate efficacy of Porcilis Lawsonia mixed with Porcilis PCV M Hyo (1253 pigs). The set-up of all these field studies was according to Ph. Eur. monograph 2448. In all the field studies, there was no statistically significant difference in level of systemic reactions, mortality and average daily body weight gain (nursery) in vaccinated groups as compared to control groups. In addition, average temperature increase was below 1.5°C in vaccinated groups in the field safety study which is agreement with Ph.Eur. monograph 2448. Although, in this study, individual temperature of four vaccinated piglets increased transiently above 2.0°C after vaccination, it returned to normal levels one day after vaccination. These piglets showed no systemic reactions and they were normal in terms of general health.

The results confirm the observations made in the laboratory studies. The local and systemic reactions observed are described in the SPC and package leaflet under “adverse reactions”.

Ecotoxicity

The applicant provided an environmental risk assessment which showed that the risk for the environment and other animals and species posed by this vaccine can be considered as very low.

Warnings and precautions as listed in the product literature for its disposal are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

In laboratory conditions, efficacy of Porcilis Lawsonia was evaluated in 12 Lawsonia challenge studies consisting of total of 14 treatment groups vaccinated with Porcilis Lawsonia as single product or in associated mixed use with Porcilis PCV M Hyo (350 pigs). Efficacy of Porcilis Lawsonia is not affected when it was used in associated mixed use with Porcilis PCV M Hyo. Therefore, the efficacy results obtained from the mixed vaccines can be considered equivalent to that of the single vaccine (Porcilis Lawsonia).

The efficacy against a Lawsonia challenge was based on the follow up of different parameters. The clinical score (diarrhea score) and the proportion of pigs with diarrhea were reduced and this reduction reached statistical significance in 7 out of 14 vaccinated groups. Faecal shedding of *Lawsonia intracellularis* was reduced in quantity and reached statistical significance in 7 of these 14 vaccinated groups for the total shedding during 3 weeks and in 10 of these 14 vaccinated groups for shedding on day 21 post-challenge. *Lawsonia intracellularis* load in ileum mucosa was also significantly reduced in 8 out of 14 vaccinated groups. Similarly, ileum scores (macroscopic and immunohistochemical stain) also showed a favourable response and 13/14 groups showed significant reduction in intestinal lesions. All vaccinated groups in these studies except one showed a significant improved weight gain compared to control animals.
The results of these 12 studies fully support the indications of Porcilis Lawsonia, i.e. to reduce
- diarrhoea,
- loss of daily weight gain,
- intestinal lesions and
- bacterial shedding

caused by *Lawsonia intracellularis* infection. The difference between vaccinated and non-vaccinated groups, in general, were statistically significant except for some single parameters in individual studies that showed favourable results but did not reach statistical significance.
Finally, the analysis of the results of mortality over all the laboratory studies show that the Lawsonia related mortality was significantly reduced in vaccinated animals compared to controls.

Taken together, all efficacy parameters showed a positive response in vaccinated animals. The absence of significant difference for single parameters in some studies is considered as acceptable as the control of a challenge can never be complete and a certain degree of variation in challenge results can be expected.

The efficacy against a *M. hyopneumoniae* challenge when Porcilis Lawsonia is mixed with Porcilis PCV M Hyo is shown in two studies. The protection against the severity of lung lesions (onset of immunity of 4 weeks and duration of immunity of 21 weeks after vaccination) is demonstrated and is in compliance with the claims of the vaccine Porcilis PCV M Hyo.

The efficacy against a porcine circovirus type 2 (PCV 2) challenge when Porcilis Lawsonia is mixed with Porcilis PCV M Hyo is shown in two studies. The efficacy claim of Porcilis PCV M Hyo which is “reduction of viraemia, virus load in lungs and lymphoid tissues, virus shedding” is demonstrated in these studies after a challenge 2 weeks post-vaccination.
Duration of immunity against PCV2 was not based on a challenge study and was determined using a serology-based efficacy study. The correlation between PCV2 antibody titre and the level of protection offered by Porcilis PCV M Hyo against PCV2 challenge has been analysed and a protective PCV2 antibody titre is used as a surrogate of the vaccine’s efficacy. In two laboratory studies, the PCV2 antibody titres of vaccinated animals (PCV M Hyo or Lawsonia + PCV M Hyo) remained well above the established protective PVC2 antibody titres for up to 24 weeks post vaccination.

The applicant has provided an analysis which shows that maternally derived antibodies against *Lawsonia intracellularis* did not have an impact on the efficacy of Porcilis Lawsonia.

In conclusion, based on the observations made in laboratory efficacy studies, it can be concluded that vaccination of pigs with Porcilis Lawsonia reduces diarrhoea, loss of daily weight gain, intestinal lesions, bacterial shedding and mortality caused by *Lawsonia intracellularis* infection. An onset of immunity of 4 weeks and duration of immunity of 21 weeks after vaccination with Porcilis Lawsonia was observed in these laboratory studies.

In conclusion, single administration of one dose (2 ml) of Porcilis Lawsonia is suitable for active immunization of pig of 3 weeks of age onwards *against L. intracellularis* infection. Porcilis Lawsonia can be administered in associated mixed use with Porcilis PCV M Hyo.

Field Trials

Four field efficacy studies were performed evaluating efficacy of Porcilis Lawsonia when used mixed with Porcilis PCV M Hyo. In these studies, efficacy of Porcilis Lawsonia against Lawsonia infection was evaluated in 3 of these 4 studies and efficacy of Porcilis PCV M Hyo against PCV2 and M hyo field infections was evaluated in 4 and 3 studies, respectively. In addition, another field efficacy study was performed in which efficacy of Porcilis Lawsonia against mortality associated with *L. intracellularis* infection (acute ileitis) was evaluated.

In all 3 field studies evaluating the efficacy of Porcilis Lawosnia a reduction in *L. intracellularis* faecal shedding was obtained; in 2 out of 3 field studies, a statistically significant reduction in LI faecal shedding was observed.
Average daily weight gain showed significant improvement in vaccinated groups compared to control groups in all four field studies with Porcilis Lawsonia + Porcilis PCV M Hyo. This favourable effect on weight could be caused by both Porcilis Lawsonia and Porcilis PCV M Hyo as field infections with more than one pathogen occurred.
For the other parameters that were followed, no statistical difference was observed.

Low level of mortality was observed in all field studies. Nevertheless, in the study with acute ileitis the mortality was significantly lower in the vaccinated group compared to the control group. In this study Porcilis Lawsonia was used to vaccinate.

In all field studies evaluating the efficacy of Porcilis PCV M Hyo mixed with Porcilis Lawsonia against PCV2 (4 studies), and M hyo (3 studies) field infections, a statistically significant protection against PCV2 and M hyo infections were observed in vaccinated animals compared to control animals.

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 the active immunisation of pigs from 3 weeks of age to reduce diarrhoea, loss of daily weight gain, intestinal lesions, bacterial shedding and mortality caused by Lawsonia intracellularis infection.

Onset of immunity: 4 weeks after vaccination.
Duration of immunity: 21 weeks after vaccination.

4.9 Amounts to be administered and administration route

Intramuscular use.
Reconstitute the lyophilisate in the solvent or in Porcilis PCV M Hyo as follows:

Lyophilisate	Solvent or Porcilis PCV M Hyo
50 doses	100 ml
100 doses	200 ml

For proper reconstitution and correct administration, use the following procedure:
1. Allow the solvent or Porcilis PCV M Hyo to reach room temperature and shake well before use.
2. Add 5-10 ml of the solvent or Porcilis PCV M Hyo to the lyophilisate and mix briefly.
3. Withdraw the reconstituted concentrate from the vial and transfer it back into the vial with the solvent or the Porcilis PCV M Hyo. Shake briefly to mix.
4. Use the vaccine suspension within 6 hours of reconstitution. Any vaccine remaining at the end of this time should be discarded.

Needle length and diameter should be adapted to the age of the animal. Avoid introduction of a contamination by multiple broaching.

Dosage:
A single dose of 2 ml of reconstituted vaccine in pigs starting at 3 weeks of age. Vaccinate pigs by the intramuscular route in the neck.

Visual appearance after reconstitution: homogenous white to nearly white emulsion after shaking.

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 benefit risk 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 (http://www.hma.eu/vmriproductindex.html).

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.