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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Porcilis Lawsonia ID lyophilisate and solvent for emulsion for injection for pigs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0424/001/DC
Name, strength and pharmaceutical form	Porcilis Lawsonia ID Lyophilisate and solvent for emulsion for injection for pigs
Applicant	Intervet International BV Wim de Körverstraat 35 5831 AN Boxmeer The NETHERLANDS
Active substances	Each dose of 0.2 ml reconstituted vaccine contains: Active substance (lyophilisate): Inactivated *Lawsonia intracellularis* strain SPAH-08 inactivated ≥ 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/

"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 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	18th November 2020
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, 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 0.2 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):

Dl-α-Tocopheryl acetate	0.6 mg
Paraffin, light liquid	8.3 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 or glass type I containers. 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
- Dl-α-Tocopheryl acetate 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 22 batches of lyophilisate and 12 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 3 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 ID alone (64 pigs) or mixed with Porcilis PCV ID (65 pigs). The safety of the intradermal administration of one dose and an overdose in the target species is demonstrated
After vaccination, a transient increase in rectal temperature was observed and rectal temperatures were back to normal on the day after vaccination. The average increase was 0.1°C with a maximum individual temperature increase of 1.4°C.
Local reactions up to 1 cm in diameter were observed in most vaccinated pigs. Maximum individual local reactions up to 5 cm in pigs vaccinated with Porcilis Lawsonia ID alone and up to 7 cm in pigs vaccinated with Porcilis Lawsonia ID in associated use with Porcilis PCV ID were observed incidentally. Local reactions disappeared within 4 weeks after 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 ID 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 0.1°C, in individual pigs up to 1.4°C). The animals return to normal temperature within 1 day after vaccination. Local injection site reactions in the form of swelling may very commonly occur (mean diameter of approximately 1 cm, in individual pigs up to 5 cm). Local reactions disappear within 4 weeks after vaccination.

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, except for protection against mortality, are available in pigs from 3 weeks of age onwards which demonstrate that this vaccine can be mixed with Porcilis PCV ID. The product literature of Porcilis PCV ID should be consulted. Adverse reactions are as described in section 4.6, except for local injection site reactions where a maximum size of up to 7 cm may occur in individual pigs. All local reactions disappear within 5 weeks after vaccination.

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product except the product 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 the local reactions described in section 4.6 were observed after the administration of a double dose of Porcilis Lawsonia ID reconstituted in solvent.

Field studies

One field safety study was designed for the purpose of collecting safety data of Porcilis Lawsonia ID (100 pigs) used alone or mixed with Porcilis PCV ID (101 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 ID (2509 pigs) alone or mixed with Porcilis PCV ID (592 pigs).

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 ID was evaluated in 14 Lawsonia challenge studies consisting of total of 18 treatment groups vaccinated with Porcilis Lawsonia ID as single product (300 pigs) or in associated mixed use with Porcilis PCV ID (150 pigs). Efficacy of Porcilis Lawsonia is not affected when it was used in associated mixed use with Porcilis PCV ID. Therefore, the efficacy results obtained from the mixed vaccines can be considered equivalent to that of the single vaccine (Porcilis Lawsonia ID).

The efficacy against a Lawsonia challenge was based on the follow up of different parameters in vaccinated and control groups. The mean diarrhea score was reduced in 7 out of 18 vaccinated groups. Faecal shedding of *Lawsonia intracellularis* was reduced in quantity and reached statistical significance in 12 of these 18 vaccinated groups for the total shedding during 3 weeks and in 10 of 18 vaccinated groups for shedding on day 21 post-challenge. *Lawsonia intracellularis* load in ileum mucosa was also significantly reduced in 10 out of 18 vaccinated groups. Similarly, ileum scores (macroscopic and immunohistochemical stain) also showed a favourable response and respectively 12/18 and 13/18 groups showed significant reduction in intestinal lesions. Thirteen vaccinated groups in these studies out of 18 showed a significant improved weight gain compared to control animals.
The results of these studies support the indications of Porcilis Lawsonia ID, 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 porcine circovirus type 2 (PCV 2) challenge when Porcilis Lawsonia ID is mixed with Porcilis PCV ID is shown in a laboratory study. The efficacy claim of Porcilis PCV ID, which is “reduction of viraemia, virus load in lungs and lymphoid tissues, virus shedding” is demonstrated in this study after a challenge 2 weeks post-vaccination.
Duration of immunity against PCV2 was determined using a serology-based efficacy study. The correlation between PCV2 antibody titre and the level of protection offered by Porcilis PCV ID against PCV2 challenge has been analysed and a protective PCV2 antibody titre is used as a surrogate of the vaccine’s efficacy. In one laboratory study, the PCV2 antibody titres of vaccinated animals (PCV ID or Lawsonia ID + PCV ID) remained well above the established protective PVC2 antibody titres for up to 24 weeks post vaccination. In two laboratory studies, a PCV infection occurred at 15 and 17 weeks after vaccination with Porcilis Lawsonia ID associated with Porcilis PCV and in both studies a significant reduction of viremia was observed in the vaccinates.

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

Based on the observations made in laboratory efficacy studies, it can be concluded that vaccination of pigs with Porcilis Lawsonia ID 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 ID was observed in these laboratory studies.

In conclusion, single administration of one dose (0.2 ml) of Porcilis Lawsonia ID is suitable for active immunization of pig of 3 weeks of age onwards *against L. intracellularis* infection. Porcilis Lawsonia ID can be administered in associated mixed use with Porcilis PCV ID.

Field Trials

Four field trials were performed evaluating efficacy of Porcilis Lawsonia ID against Lawsonia field infection when used as a single vaccine and in associated mixed use with Porcilis PCV ID (in 2 studies). Furthermore, in these studies, efficacy of Porcilis PCV ID against PCV2 field infection was also evaluated.

The level of Lawsonia infections were very low and as such provide limited information on field efficacy of the vaccine. In one study, average daily weight gain showed significant improvement in vaccinated group with Porcilis Lawsonia ID + Porcilis PCV ID compared to control group.
For the other parameters that were followed, no statistical difference was observed in the different studies.

In addition, another field efficacy study was performed in which the efficacy of Porcilis Lawsonia ID against mortality caused by *L. intracellularis* infection (acute ileitis) was evaluated. The overall mortality and Lawsonia infection (acute ileitis) associated mortality was significantly reduced in Porcilis Lawsonia ID vaccinated groups.

In the two field studies evaluating the efficacy of Porcilis PCV ID mixed with Porcilis Lawsonia ID against PCV2 field infections, statistically significant protection against PCV2 infections was 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.

4.8 Interaction with other medicinal products and other forms of interaction

Safety and efficacy data, except for protection against mortality, are available in pigs from 3 weeks of age onwards, which demonstrate that this vaccine can be mixed with Porcilis PCV ID. The product literature of Porcilis PCV ID should be consulted. Adverse reactions are as described in section 4.6, except for local

injection site reactions where a maximum size of up to 7 cm may occur in individual pigs. All local reactions disappear within 5 weeks after vaccination.

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product except the product 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.

4.9 Amounts to be administered and administration route

Intradermal use.

Reconstitute the lyophilisate in the solvent or in Porcilis PCV ID as follows:

Lyophilisate	Solvent for Porcilis Lawsonia ID or Porcilis PCV ID
50 doses	10 ml
100 doses	20 ml

For proper reconstitution and correct administration, use the following procedure:

1. *Allow the solvent or Porcilis PCV ID to reach room temperature and shake well before use.*
2. *Add approximately 5-10 ml of the solvent or Porcilis PCV ID to the lyophilisate vial 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 ID. 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.*

Avoid introduction of a contamination by multiple broaching.

Dosage:
A single dose of 0.2 ml of reconstituted vaccine in pigs starting at 3 weeks of age.

Vaccinate pigs by the intradermal route using a multi-dose needle-free injection device for intradermal application of liquids suitable to deliver a "jet-stream" volume of vaccine (0.2ml ± 10%) through the epidermal layers of the skin.

Safety and efficacy of Porcilis Lawsonia ID have been demonstrated using the device IDAL.

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.