Paul-Ehrlich-Institut

# Beurteilungsbericht zur Veröffentlichung

(gemäß § 31 Abs. 2 Tierimpfstoff-Verordnung)

## Porcilis Ery+Parvo+Lepto

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|---|---|
| Zulassungsdatum: | 01.09.2016 |
| Zulassungsnummer: | PEI.V.11798.01.1 |
| Datum der Erstellung des öffentlichen Beurteilungsberichts: | 07.10.2016 |
| Datum der Bekanntgabe beim Antragsteller der/des Zulassungsänderung/Widerrufs, Rücknahme, Anordnung des Ruhens der Zulassung: | |

Paul-Ehrlich-Institut
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

**Paul-Ehrlich-Institut**
**Paul-Ehrlich-Straße 51-59**
**63225 Langen**
**(Reference Member State)**

**DECENTRALISED PROCEDURE**

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## Porcilis Ery+Parvo+Lepto

**PRODUCT SUMMARY**

| | |
|---|---|
| EU Procedure number | DE/V/0268/001/DC |
| Name, strength and pharmaceutical form | Porcilis Ery+Parvo+Lepto,<br>suspension for injection for pigs |
| Applicant | Intervet Deutschland GmbH<br>Feldstraße 1a<br>85716 Unterschleißheim<br>Germany |
| Active substance(s) | <u>Active substances (inactivated) per dose (2 ml)</u><br>*Erysipelothrix* (*E.*) *rhusiopathiae*, serotype 2,strain M2,<br>≥ 1 ppd*<br>Porcine parvovirus, strain 014,<br>≥ 130 U**<br>*Leptospira (L.) interrogans* serogroup Canicola serovar Portland-Vere, strain Ca-12-000,<br>≥ 2816 U**<br>*L. interrogans* serogroup Icterohaemorrhagiae serovar Copenhageni, strain Ic-02-001,<br>≥ 210 U**<br>*L. interrogans* serogroup Australis serovar Bratislava, strain As-05-073,<br>≥ 1704 U**<br>*L. kirschneri* serogroup Grippotyphosa serovar Dadas, strain Gr-01-005,<br>≥ 648 U**<br>*L. interrogans* serogroup Pomona serovar Pomona, strain Po-01-000,<br>≥ 166 U**<br>*L. santarosai* serogroup Tarassovi serovar Gatuni, strain S1148/02,<br>≥ 276 U**<br><br>*Pig protective dose as compared to a reference preparation known to be protective in pigs.<br>**As determined in the in vitro antigenic mass ELISA potency test.<br><br><u>Adjuvant:</u><br>dl-α-tocopheryl acetate, 150 mg<br><br>Excipient:<br>Formaldehyde (preservative), 0.4 – 1 mg |
| ATC Vetcode | QI09AL07 |

| | |
|---|---|
| Target species | Pig for reproduction |
| Indication for use | For the active immunization of pigs<br>- to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by *Erysipelothrix rhusiopathiae*, serotype 1 and serotype 2.<br>- to reduce transplacental infection, viral load and foetal mortality caused by porcine parvovirus.<br>- to reduce clinical signs (increase of body temperature and reduction in feed intake or activity), infection and bacterial excretion caused by *L. interrogans* serogroup Canicola serovar Canicola.<br>- to reduce clinical signs (increase of body temperature and reduction in feed intake or activity), severity of infection and foetal mortality caused by *L. interrogans* serogroup Pomona serovar Pomona.<br>- to reduce infection caused by *L. interrogans* serogroup Icterohaemorrhagiae serovars Copenhageni and Icterohaemorrhagiae, *L. interrogans* serogroup Australis serovar Bratislava, *L. kirschneri* serogroup Grippotyphosa serovars Grippotyphosa and Bananal/Liangguang, *L. weilii* serogroup Tarassovi serovar Vughia and *L. borgpetersenii* serogroup Tarassovi serovar Tarassovi. |

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Porcilis Ery+Parvo+Lepto suspension for injection for pigs

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 2 ml contains:

**Active substances:**

| | |
|---|---|
| Inactivated strains of: | |
| *Erysipelothrix rhusiopathiae*, serotype 2 (strain M2) | ≥ 1 ppd[1] |
| Porcine parvovirus (strain 014) | ≥ 130 U[2] |
| *Leptospira interrogans* serogroup Canicola serovar Portland-Vere (strain Ca-12-000) | ≥ 2816 U[2] |
| *Leptospira interrogans* serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) | ≥ 210 U[2] |
| *Leptospira interrogans* serogroup Australis serovar Bratislava (strain As-05-073) | ≥1704 U[2] |
| *Leptospira kirschneri* serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) | ≥ 648 U[2] |
| *Leptospira interrogans* serogroup Pomona serovar Pomona (strain Po-01-000) | ≥ 166 U[2] |
| *Leptospira santarosai* serogroup Tarassovi serovar Gatuni (strain S1148/02) | ≥ 276 U[2] |

**Adjuvant:**

| | |
|---|---|
| dl-α-tocopheryl acetate | 150 mg |

**Excipient:**

| | |
|---|---|
| Formaldehyde (preservative) | 0.4-1 mg |

[1] Pig protective dose as compared to a reference preparation known to be protective in pigs.
[2] As determined in the *in vitro* antigenic mass ELISA potency test.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Suspension for injection.
Homogenous white to nearly white suspension after shaking.

## 4. CLINICAL PARTICULARS

### 4.1 Target species

Pig for reproduction.

### 4.2 Indications for use, specifying the target species

For the active immunization of pigs:

- to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by *Erysipelothrix rhusiopathiae*, serotype 1 and serotype 2.
- to reduce transplacental infection, viral load and foetal mortality caused by Porcine parvovirus.
- to reduce clinical signs (increase of body temperature and reduction in feed intake or activity), infection and bacterial excretion caused by *L. interrogans* serogroup Canicola serovar Canicola.
- to reduce clinical signs (increase of body temperature and reduction in feed intake or activity), severity of infection and foetal mortality caused by *L. interrogans serogroup* Pomona serovar Pomona.
- to reduce infection caused by *L. interrogans* serogroup Icterohaemorrhagiae serovars Copenhageni and Icterohaemorrhagiae, *L. interrogans* serogroup Australis serovar Bratislava, *L. kirschneri* serogroup Grippotyphosa serovars Grippotyphosa and Bananal/Liangguang, *L. weilii* serogroup Tarassovi serovar Vughia and *L. borgpetersenii* serogroup Tarassovi serovar Tarassovi.

Onset of Immunity:
*E. rhusiopathiae*: 3 weeks
Porcine parvovirus: 10 weeks
*Leptospira* serogroups: 2 weeks

Duration of Immunity:
*E. rhusiopathiae*: 6 months
Porcine parvovirus: 12 months
*Leptospira* serogroup Australis: 6 months
*Leptospira* serogroups Canicola, Icterohaemorrhagiae, Grippotyphosa, Pomona and Tarassovi: 12 months

**4.3 Contraindications**
None.

**4.4 Special warnings for each target species**
None.

**4.5 Special precautions for use**
Special precautions for use in animals
Vaccinate only healthy animals.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

**4.6 Adverse reactions (frequency and seriousness)**
Transient local reactions, mostly consisting of red, mild to hard, non-painful swellings are a very common observation. In general, local reactions may have a diameter of ≤ 5 cm, in very rare cases local reactions in individual animals can be up to 20 cm in diameter. All local reactions disappear completely within approximately 2 weeks after vaccination. In individual animals intermediate systemic reactions, such as vomiting, redness, rapid breathing and twitching, may rarely be observed, which resolve in a few minutes. In individual animals transient reductions in feed intake or activity may uncommonly occur. Feed intake and activity are completely restored within a week. An increase in body temperature may very commonly occur up until two days after vaccination. The observed mean increase was 0.5°C (in individual cases the maximum increase was 1.5°C).

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

**4.7 Use during pregnancy, lactation or lay**
Can be used during pregnancy and lactation.

**4.8 Interaction with other medicinal products and other forms of interaction**
No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. 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**
Before use allow the vaccine to reach room temperature.
Shake well before use.
Avoid introduction of contamination.

For intramuscular use.
Administer a single dose of 2 ml in the neck region.

Basic vaccination scheme: Pigs which have not yet been vaccinated shall be given a primary injection 6 to 8 weeks before the expected date of insemination and a booster injection 4 weeks later.

Revaccination: A single revaccination with the veterinary medicinal product should be given once a year. Six months post each vaccination with the veterinary medicinal product, a single revaccination with an *Erysipelotrix rhusiopathiae* containing product should be given to maintain immunity against *Erysipelotrix rhusiopathiae*. In case of known infection pressure with *L. interrogans* serogroup Australis, a single revaccination with the veterinary medicinal product should be given every six months, as it is unknown if or for how long the duration of immunity for this serogroup persists beyond six months.

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

No adverse reactions other than those mentioned in section 4.6 were observed after the administration of a double dose of vaccine.

**4.11 Withdrawal period(s)**

Zero days.

## 5. IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Immunologicals for Suidae. Inactivated viral and inactivated bacterial vaccine for pigs. ATC vet code: QI09AL07.

The product stimulates the development of active immunity in pigs against *E. rhusiopathiae*, Porcine parvovirus, *L. interrogans* serogroup Canicola serovar Canicola, *L. interrogans* serogroup Icterohaemorrhagiae serovars Copenhageni and Icterohaemorrhagiae, *L. interrogans* serogroup Australis serovar Bratislava, *L. kirschneri* serogroup Grippotyphosa serovars Grippotyphosa and Bananal/Liangguang, *L. interrogans* serogroup Pomona serovar Pomona, *L. weilii* serogroup Tarassovi serovar Vughia and *L. borgpetersenii* serogroup Tarassovi serovar Tarassovi.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Formaldehyde
dl-α-tocopheryl acetate
Polysorbate 80
Simethicone
Sodium chloride
Potassium Chloride
Potassium dihydrogen phosphate
Disodium phosphate dihydrate
Water for injection

**6.2 Incompatibilities**

Do not mix with any other veterinary medicinal product.

**6.3 Shelf life**

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 10 hours.

**6.4. Special precautions for storage**

Store in a refrigerator (2°C–8°C).
Do not freeze.
Protect from light.

**6.5 Nature and composition of immediate packaging**

PET vials of 20 ml (10 doses), 50 ml (25 doses), 100 ml (50 doses) or 250 ml (125 doses) are closed with a halogenobutyl rubber stopper (type I, Ph. Eur.) and sealed with an aluminium cap.

Pack size:
Cardboard box with 1 vial of 20 ml.
Cardboard box with 10 vials of 20 ml.
Cardboard box with 1 vial of 50 ml.
Cardboard box with 10 vials of 50 ml.
Cardboard box with 1 vial of 100 ml.
Cardboard box with 1 vial of 250 ml.

Not all pack sizes may be marketed.

**6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products**

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Intervet International B.V., as represented by the national company
Wim de Körverstraat 35
5831 AN Boxmeer
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: {DD/MM/YYYY}.

**10. DATE OF REVISION OF THE TEXT**

{MM/YYYY}

**PROHIBITION OF SALE, SUPPLY AND/OR USE**

Not applicable.

**PUBLIC ASSESSMENT REPORT**

| | |
|---|---|
| Legal basis of original application | Decentralised application in accordance with Article 32 (3) of Directive 2001/82/EC as amended. |
| Date of completion of the original decentralised procedure | 27th July 2016 |
| Date product first authorised in the Reference Member State (MRP only) | Not applicable. |
| Concerned Member States for original procedure | Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, United Kingdom |

# I. SCIENTIFIC OVERVIEW

Porcilis Ery+Parvo+Lepto is an inactivated vaccine which is indicated for the immunisation of healthy sows and gilts six to eight weeks before the expected date of insemination against swine Erysipelas, porcine parvovirus (PPV) infection and Leptospirosis. The vaccine contains dl-α-tocopheryl acetate as adjuvant. Formaldehyde is added as a preservative. The vaccine is presented as suspension for injection in multidose containers with a respective dose volume of 2 ml.

The product is produced and controlled using validated methods and tests, which ensure the consistency of the released product 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, the consumer of foodstuffs from treated animals and for the environment, when used as recommended.

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

Each dose of 2 ml contains:

**Active substances:**

| | |
|---|---|
| Inactivated strains of: | |
| *Erysipelothrix rhusiopathiae*, serotype 2 (strain M2) | ≥ 1 ppd[1] |
| Porcine parvovirus (strain 014) | ≥ 130 U[2] |
| *Leptospira interrogans* serogroup Canicola serovar Portland-Vere (strain Ca-12-000) | ≥ 2816 U[2] |
| *Leptospira interrogans* serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) | ≥ 210 U[2] |
| *Leptospira interrogans* serogroup Australis serovar Bratislava (strain As-05-073) | ≥1704 U[2] |
| *Leptospira kirschneri* serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) | ≥ 648 U[2] |
| *Leptospira interrogans* serogroup Pomona serovar Pomona (strain Po-01-000) | ≥ 166 U[2] |
| *Leptospira santarosai* serogroup Tarassovi serovar Gatuni (strain S1148/02) | ≥ 276 U[2] |

[1] Pig protective dose as compared to a reference preparation known to be protective in pigs.

[2] As determined in the *in vitro* antigenic mass ELISA potency test.

**Adjuvant:**

| | |
|---|---|
| dl-α-tocopheryl acetate | 150 mg |

**Excipient:**

| | |
|---|---|
| Formaldehyde (preservative) | 0.4-1 mg |

Container/closure system:
The vaccine is presented in polyethylene terephthalate (PET) vials of 20, 50, 100 or 250 ml.
Neither the European Pharmacopoeia nor the USP include a specific monograph on PET containers intended for the primary packaging of injectables. A specific monograph on PET vials intended for packaging liquid oral dosage forms is described in the USP. The tests described in this specific USP chapter fulfil the general requirements for plastic containers for pharmaceuticals described in the European Pharmacopoeia 3.2.2. The PET container is classified as a Plastic Class VI. This means that the plastic material meets all the USP requirements as described in the sections “Biological tests - plastics” and “Physicochemical tests - plastics”.
Vials are closed with a halogenobutyl rubber stopper (Ph.Eur. 3.2.9) and sealed with an aluminium cap.

The choice of the adjuvant (dl-α-tocopheryl acetate) and the vaccine strains (*Erysipelothrix rhusiopathiae,* porcine parvovirus*, Leptospira (L.)* Icterohaemorrhagiae, *L.* Canicola, *L.* Grippotyphosa, *L*. Pomona, *L.* Tarassovi and *L.* Australis) are justified.

The inactivation process and the detection limit of the control of inactivation 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 Practice (GMP) from a licensed manufacturing site. A corresponding manufacturing licence and GMP certificates are provided.
Process validation data on the product have been presented in accordance with the relevant European guidelines.
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 the pharmacopoeia monograph 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).
Seed lots and cell banks have been produced as described in the relevant guideline.

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.

## D. Control tests during production

The tests performed during production are described and the results of three consecutive runs, conforming to the specifications, are provided.
These tests are as follows:

*Erysipelothrix rhusiopathiae:*
- Growth and purity
- Determination of cell weight
- Demonstration of inactivation
- Sterility

Porcine parvovirus:
- Haemagglutination assay before virus inactivation
- Demonstration of inactivation
- Sterility
- Determination of antigen mass

*Leptospira:*
- Growth and purity
- Bacterial count
- Demonstration of inactivation
- Sterility

The applicant presented in-process data for consecutive antigen batches.
During the manufacture of the antigens the above mentioned tests are carried out.
The filling volume is controlled during the manufacture of the finished product.
Test descriptions and the limits of acceptance were presented. The relevant test methods for in-process controls are satisfactorily validated.

## E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements.
These tests are as follows:

- Determination of pH
- Determination of formaldehyde concentration
- Appearance
- Sterility: according to Ph.Eur. 2.6.1
- Determination of dl-α-tocopheryl acetate concentration
- Test on filling volume
- Potency of *E. rhusiopathiae*, PPV and *Leptospira*
- Extraneous agents

The demonstration of the batch to batch consistency is based on the results of three batches produced according to the method described in the dossier.

The applicant presented data for three consecutive finished product batches.
The above mentioned tests are performed.
Test descriptions and limits of acceptance are presented. The control methods are satisfactorily validated or clarification is provided in order to confirm that the production and control processes generate consistent vaccine batches.

## F. 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 (2 years) when stored under the approved conditions (at 2-8° C).

The shelf life of the vaccine after broaching the immediate packaging is 10 hours. The claim of a 10 hour stability after broaching is based on the demonstration of stability for a batch broached and stored at 30 °C for 3 days.

## G. Other Information

Two batches of the vaccine at 39 months after start of shelf life were tested for bacteria (*S. aureus*, *P. aeruginosa*) and fungi (*C. albicans*, *A. niger*) to demonstrate adequately the efficacy of the preservative.

## III. SAFETY ASSESSMENT

The safety of the product has been demonstrated in laboratory studies in accordance with the following guidelines and Ph.Eur. monographs:

- Guidance on the safety testing of veterinary vaccines is provided by Directive 2001/82, Annex I, Title II as amended by Directive 2004/28/EC.
- Guidance on the safety of vaccines in general: Ph. Eur. 5.2.6: Evaluation of safety of veterinary vaccines and immunosera
- Erysipelas: Ph. Eur. Monograph 0064 (Swine erysipelas vaccine [inactivated])
- Porcine parvovirosis: Ph. Eur. Monograph 0965 (Porcine parvovirosis vaccine [inactiv.]
- Leptospirosis: Ph. Eur. Monographs 0062 (Vaccines for veterinary use), as no Ph. Eur. monograph exists for Leptospirosis in pigs

Vaccine batches used in the safety studies were produced as described in the dossier and met all relevant release requirements.

### Laboratory trials (Pre-clinical studies)

**Porcilis Ery+Parvo+Lepto** is an inactivated multivalent vaccine for the active immunisation of pigs against swine Erysipelas, porcine parvovirus infection and Leptospirosis. The vaccine is intended for intramuscular injection of sows and gilts six to eight weeks before the expected date of insemination and a booster injection four weeks later.

The trials have been performed in the target species (pigs).
All animals used were seronegative to the individual antigens.

The safety of the administration of one dose, an overdose (double dose), the repeated administration of one dose in young gilts and in pregnant gilts was demonstrated in laboratory trials.

Safety study 1: The animals were allocated to different groups and were administered either a single dose, an overdose or repeat single doses at intervals of two or four weeks. Unvaccinated animals were used as control group. All animals were monitored for local and systemic reactions during the study. The pigs remained healthy after the vaccinations and no clinical/ systemic reactions in the vaccination groups were observed. No local reactions were observed except for two animals.
Safety study 2: The pregnant gilts were allocated to different groups and were administered a double dose followed by two repeated single doses at intervals of two or four weeks. Unvaccinated animals were used as control group. In this study the vaccine safety during pregnancy and for the offspring were determined in addition to local and systemic reactions. The pigs remained healthy after the vaccinations and no clinical/systemic reactions in the vaccination groups were observed except for one gilt, and about half of the animals showed local reactions. The examination of the effects on reproductive performance shows that **Porcilis Ery+Parvo+Lepto** can be safely used in pregnant gilts. A corresponding note is included in the SPC and package leaflet.

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

**Porcilis Ery+Parvo+Lepto** is an inactivated vaccine. There is no reason to suppose that it might adversely affect immunological functions of the vaccinated animal or its progeny. Therefore, specific tests on the impact of vaccination with **Porcilis Ery+Parvo+Lepto** on immunological functions of the pigs were not performed. Given the experience with the inactivated components of this vaccine, no adverse influences on the immune functions are expected.

**Porcilis Ery+Parvo+Lepto** contains only inactivated antigens and thus the specific tests to be performed for live vaccines are not applicable.

No information is available on the safety of this vaccine when used with any other veterinary medicinal product. 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.
The adjuvant components dl-α-tocopheryl acetate and all excipients used are considered to be safe because they are mentioned in Table 1 of Commission regulation 37/2010 requiring no MRL insert status with reference to MRL regulations. Based on this information, no withdrawal period is proposed.

## Field studies (Clinical trials)

Five combined field safety and efficacy studies were conducted in Germany (553 sows and gilts), in the UK (676 sows and gilts), in Hungary (506 sows and gilts), in France (223 sows and gilts) and in Portugal (1783 sows and gilts), respectively. The studies focused on the *Leptospira* components, since the *E. rhusiopathiae* and PPV components are well known and have been studied in the field before. During these studies the pigs were observed for possible side effects after vaccination.
The field studies were performed in compliance with VICH guideline “Good Clinical Practice” GL No. 9 and the applicable Standard Operating Procedures. The farms were chosen for their sub-optimal reproduction status, which was assumed to be related to Leptospira infection (based on positive serology in part of the animals).
The results of the studies confirm the safety of Porcilis Ery+Parvo+Lepto for breeding pigs.
Low incidences of systemic reactions related to vaccination were observed and the incidence and severity of local reactions were similar to those of the control product Porcilis Ery+Parvo.
As regards rectal temperature, no clinically relevant effect was observed.
The similar reproductive performance of the vaccination groups in the safety period (from 1st vaccination until the onset of immunity three weeks after second vaccination) supports the conclusion that the safety profile of Porcilis Ery+Parvo+Lepto is comparable to that of the reference product, Porcilis Ery+Parvo.

In conclusion, systemic reactions which resolve within a few minutes may be observed in rare cases. In very rare cases a transient reduction in feed intake or activity, may occur in individual animals. These animals completely recover within one week.
A mean transient increase in body temperature of about 0.5°C may very commonly occur up until two days after vaccination. It can increase up to 1.5°C in single cases.
Observed local reactions are very common and may have a diameter of ≤ 5 cm, in very rare cases local reactions in individual animals can be up to 20 cm in diameter. All local reactions disappear completely within approximately two weeks after vaccination.
The examination of the effects on reproductive performance shows that **Porcilis Ery+Parvo+Lepto** can be safely used in pregnant gilts.

Overall, **Porcilis Ery+Parvo+Lepto** vaccine proved to be well tolerated in the target species pig, and it can be concluded that Porcilis Ery+Parvo+Lepto can be safely used in gilts from 16-weeks-old and in pregnant gilts/sows when using the recommended vaccination schemes and the recommended route of administration. The local and systemic reactions observed are described in the SPC (Summary of Product Characteristics) and package leaflet under "adverse reactions" (section 4.6 and section 6, respectively).

### Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that all hazards identified have a negligible likelihood and therefore assessment of the consequences is not necessary.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

## IV. EFFICACY

### IV.B Laboratory Trials (Pre-clinical studies)

The efficacy of the product has been demonstrated in laboratory studies in accordance with the following guidelines and Ph.Eur. monographs:

- Guidance on the efficacy testing of veterinary vaccines is provided by Directive 2001/82, Annex I, Title II as amended by Directive 2004/28/EC.
- Guidance on the safety of vaccines in general: Ph. Eur. 5.2.: Evaluation of efficacy of veterinary vaccines and immunosera
- Guideline EMEA/CVMP/IWP/123243/2006 Rev. 2 on "Data requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets" for the *Leptospira* components
- Erysipelas: Ph. Eur. Monograph 0064 (Swine erysipelas vaccine [inactivated])
- Porcine parvovirosis: Ph. Eur. Monograph 0965 (Porcine parvovirosis vaccine [inactiv.]
- Leptospirosis: Ph. Eur. Monographs 0062 (Vaccines for veterinary use), as no Ph. Eur. monograph exists for Leptospirosis in pigs

Vaccine batches used in the efficacy studies were produced as described in the dossier and met all relevant release requirements.

A number of laboratory challenge studies were performed in young pigs to evaluate the efficacy of Porcilis Ery+Parvo+Lepto. In these trials, seronegative animals were vaccinated with **Porcilis Ery+Parvo+Lepto** and subsequently challenged with two *E. rhusiopathiae* challenge strains, two porcine parvovirus challenge strains and nine different *Leptospira* challenge strains. Unvaccinated animals served as controls.

To evaluate dose response, onset of immunity and duration of immunity for the *E. rhusiopathiae* component in Porcilis Ery+Parvo+Lepto the applicant performed three studies in which 40 vaccinates and 30 control animals were involved. From the results of these studies it can be concluded that after completion of the basic vaccination with Porcilis Ery+Parvo+Lepto a complete protection against clinical signs caused by both *E. rhusiopathiae*

serotype 1 and serotype 2 was induced three weeks after vaccination. Six month after completion of the vaccination schedule the study results showed that Porcilis Ery+Parvo+Lepto induced a significant reduction of clinical signs caused by *E. rhusiopathiae* serotype 1 and serotype 2. Therefore, the claim for reduction of clinical signs for the *Erysipelothrix rhusiopathiae* component and the duration of immunity of 6 months is acceptable.

To evaluate dose response, onset of immunity and duration of immunity for the porcine parvovirus component in **Porcilis Ery+Parvo+Lepto** the applicant performed five studies in which 82 vaccinates and 33 control animals were involved.
In all five studies, a significant reduction in PPV-specific mortality could be demonstrated, however the studies provided initially did not meet one of the validity requirements of Ph. Eur. Monograph 0965 (≥90% controls infected). Upon request, the applicant re-tested samples by qPCR of two studies, which were already presented in the original dossier, and one new study, which evaluated dose response and onset of immunity of the PPV component of Porcilis Ery+Parvo+Lepto. Two of the three studies fully comply with Ph. Eur. Monograph 0965 and are therefore acceptable. In addition to the significant reduction in PPV-specific mortality, a statistically significant reduction of transplacental infection and viral loads could also be shown for all three studies in which the samples were tested by qPCR. Therefore, the proposed onset of immunity of 10 weeks and duration of immunity of 12 months after complete vaccination is acceptable.

Seven dose response studies and six duration of immunity studies were performed for the *Leptospira* components in which 300 vaccinates and 240 control animals were involved. The duration of immunity of 12 months for *Leptospira* serogroups Canicola, Icterohaemorrhagiae, Grippotyphosa, Pomona and Tarassovi is supported by the studies. For *Leptospira* serogroup Australis only a duration of immunity of six months could be shown. Upon request the applicant has commented on this taking into consideration the proposed immunisation scheme with a single revaccination for all *Leptospira* serogroups once a year. It is proposed that “in case of expected *L*. interrogans serogroup Australis problems, a single revaccination with Porcilis Ery+Parvo+Lepto should be given every six months”. The claim that immunisation with Porcilis Ery+Parvo+Lepto induces active immunization of pigs against reproductive problems caused by *L*. interrogans serogroup Pomona serovar Pomona was acceptable. Based on the performed studies, the claim for reduction of clinical signs caused by *L*. serogroup Canicola and Pomona, the claim for reduction of infection as regard all *Leptospira* serogroups and the claim for reduction in shedding for the *Leptospira* serogroup Canicola is supported.

Maternally derived antibodies were not investigated, because the vaccination age of 6 to 8 weeks before the expected date of insemination excludes any interactions of such antibodies with any of the components of the vaccine.

The dose-response studies were performed for *E. rhusiopathiae* with 12-week-old gilts and for the parvovirus component with 5-month-old gilts which is almost in compliance with the age of vaccination recommended in the SPC. In contrast, for the *Leptospira* components the dose-response studies were performed with 6-week-old pigs which were not in compliance with the recommended age of vaccination. Subsequently, a detailed and sufficient explanation relating the age of pigs used for the dose response and onset/duration of immunity studies for the different components of the vaccine was provided.

For evaluation of the effect of re-vaccination after one year after primary vaccination a study with nine sows has been conducted. In this study a single dose re-vaccination with Porcilis Ery+Parvo+Lepto, one year after the primary vaccination course, was sufficient to boost serum titres against all six *Leptospira* serogroups to similar levels, and against *E. rhusiopathiae* and parvovirus to even higher titres, than those measured after primary vaccination. Based on the generated data, it can be concluded that a single annual re-vaccination with **Porcilis Ery+Parvo+Lepto** is sufficient to restore full immunity.

The results demonstrate the efficacy of **Porcilis Ery+Parvo+Lepto**.

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

For the active immunization of pigs:

- to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by *Erysipelothrix rhusiopathiae*, serotype 1 and serotype 2.
- to reduce transplacental infection, viral load and foetal mortality caused by porcine parvovirus.
- to reduce clinical signs (increase of body temperature and reduction in feed intake or activity), infection and bacterial excretion caused by *L. interrogans* serogroup Canicola serovar Canicola.
- to reduce clinical signs (increase of body temperature and reduction in feed intake or activity), severity of infection and foetal mortality caused by *L. interrogans* serogroup Pomona serovar Pomona.
- to reduce infection caused by *L. interrogans* serogroup Icterohaemorrhagiae serovars Copenhageni and Icterohaemorrhagiae, *L. interrogans* serogroup Australis serovar Bratislava, *L. kirschneri* serogroup Grippotyphosa serovars Grippotyphosa and Bananal/Liangguang, *L. weilii* serogroup Tarassovi serovar Vughia and *L. borgpetersenii* serogroup Tarassovi serovar Tarassovi.

Onset of immunity: Immunity has been demonstrated from three weeks after completion of the primary course for *E. rhusiopathiae*, 10 weeks after completion of the primary course for porcine parvovirus and from two weeks after the primary course for *Leptospira* serogroups.

Duration of immunity: At least one year following the primary vaccination course for porcine parvovirus and *Leptospira* serogroups Canicola, Icterohaemorrhagiae, Grippotyphosa, Pomona and Tarassovi. For *E. rhusiopathiae* and *Leptospira* serogroup Australis six months following the primary vaccination course has been demonstrated.

Vaccination scheme:

For intramuscular use.
Administer a single dose of 2 ml in the neck region.

Basic vaccination scheme: Pigs which have not yet been vaccinated shall be given a primary injection six to eight weeks before the expected date of insemination and a booster injection 4 weeks later.

Revaccination: A single revaccination with the veterinary medicinal product should be given once a year. Six months post each vaccination with the veterinary medicinal product, a single revaccination with an *Erysipelotrix rhusiopathiae* containing product should be given to maintain immunity against *Erysipelotrix rhusiopathiae*. In case of known infection pressure with *L. interrogans* serogroup Australis, a single revaccination with the veterinary medicinal product should be given every six months, as it is unknown if or for how long the duration of immunity for this serogroup persists beyond six months.

### Field Trials (Clinical trials)

Five combined field safety and efficacy studies were conducted in Germany (553 sows and gilts), in the UK (676 sows and gilts), in Hungary (506 sows and gilts), in France (223 sows and gilts) and in Portugal (1783 sows and gilts), respectively.
From the field studies it can be concluded that the serological response for the *E. rhusiopathiae* and parvovirus component in Porcilis Ery+Parvo+Lepto is not negatively influenced by the Leptospira components. No further conclusions can be drawn concerning the efficacy of Porcilis Ery+Parvo+Lepto against Leptospirosis, because no or not sufficiently high field infection was observed.

## 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.

## POST-AUTHORISATION PROCEDURES

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/labelling/package leaflet are available in the Union Product Database (UPD).

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

### Sequence of significant variations

| **Summary of change (Application number)** | **Approval date** |
|---|---|
| Introduction of an end of-shelf life limit of 1310 U/dose for the Leptospira Australis component of Porcilis Ery+Parvo+Lepto vaccine Example: Change in shelf-life<br>(**DE/V/0268/001/II/002**) | 03 May 2028 |
| Harmonisation of the porcine parvovirus antigen shelf life to 24 months in all member states, Removal of formaldehyde as a preservative from the finished product, Deletion of manufacturing sites for the PPV active substance<br>**(DE/V/0268/001/II/004/G)** | 05 September 2019 |
| Addition of MSD AH Danube Biotech GmbH, Krems, Austria as production site for *E. rhusiopathiae* antigen, Increase in the *E. rhusiopathiae* antigen batch size from 2000 L to 3000 L, Minor updates to the currently licensed antigen production process for *E. rhusiopathiae*<br>**(DE/V/0268/001/A/008/G)** | 11 December 2022 |
| Alignment of the product information of Porcilis Ery+Parvo+Lepto to the current QRD v.9 template<br>**(DE/V/0268/001/A/009)** | 25 June 2023 |