



College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

**Graadt van Roggenweg 500
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The Netherlands**

DECENTRALISED PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

FIXR APP 2,9,11 emulsion for injection for pigs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0430/001
Name, strength and pharmaceutical form	FIXR APP 2,9,11 emulsion for injection for pigs
Applicant	Kernfarm B.V. De Corridor 14D 3621 ZB Breukelen, Utrecht The Netherlands
Active substance(s)	<i>Actinobacillus pleuropneumoniae</i> serovar 2 <i>Actinobacillus pleuropneumoniae</i> serovars 9,11 toxoid APX I toxoid APX II toxoid APX III
ATC Vetcode	QI09AB07
Target species	Pigs
Indication for use	For active immunisation of fattening pigs from 6 weeks of age onwards to reduce lung lesions and to reduce colonisation of the respiratory tract by <i>Actinobacillus pleuropneumoniae</i> – the causative agent of pleuropneumonia in pigs.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (<http://www.HMA.eu>).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	DECENTRALISED PROCEDURE application in accordance with Article 32(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	13/06/2019
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	Belgium (BE), Netherlands (NL) (CZ was the former RMS, procedure number CZ/V/0158/001)

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.

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. *Qualitative and quantitative particulars*

The product contains

Active substances:

<i>Actinobacillus pleuropneumoniae</i> serovar 2	RP ≥ 1*
<i>Actinobacillus pleuropneumoniae</i> serovars 9, 11	RP ≥ 1*
toxoid APX I	RP ≥ 1*
toxoid APX II	RP ≥ 1*
toxoid APX III	RP ≥ 1*

*RP = Relative potency (ELISA test) in comparison with the reference serum obtained after vaccination of mice with a vaccine batch that has successfully passed the challenge test in the target species.

List of excipients:

Oil emulsion Montanide ISA 35 VG
Formaldehyde
Thiomersal
Sodium chloride

Water for injection

The vaccine is presented:

in glass injection vials of hydrolytic class I: 10-ml vial with a content of 10 ml
in glass injection vials of hydrolytic class II: 50-ml vial with a content of 50 ml
100-ml vial with a content of 100 ml

in plastic injection vials: 15-ml vial with a content of 10 ml
60-ml vial with a content of 50 ml
120-ml vial with a content of 100 ml

in plastic bottles: 250-ml bottle with a content of 250 ml

Vials or bottles are hermetically closed with a rubber stopper for perforation and an aluminium seal and placed to paper cartons or in plastic box with 10 wells.

Pack sizes: 1 x 10 ml, 10 x 10 ml, 1 x 50 ml, 1 x 100 ml, 1 x 250 ml

The particulars of the containers and controls performed are provided and conform to the regulation of monographs 3.2.1 and 3.2.9 of the European Pharmacopoeia.

The choice of the vaccine strains, of the vaccine composition, adjuvant, inactivating agent, preservative, of the dose volume and vaccination schedule 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 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

The active substances are inactivated strains *Actinobacillus pleuropneumoniae* serovars 2, 9, 11 and toxoids APX I, APX II and APX III which are established active substances. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Starting materials of non-biological origin used in production comply with indicate pharmacopoeia monographs 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 monographs and European guidelines, 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 and satisfactorily tested according to current European requirements.

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.

D. Control tests during production

The tests performed during production (purity control, density control, determination of APX I, II, III toxins in bacterial culture, inactivation control, bacterial endotoxins, sterility test, pH determination, thiomersal) are described in detail and the results of 3 consecutive runs, conforming to the specifications, are provided.

E. 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. Relevant validations are provided.

The tests include in particular:

- appearance
- extractable volume
- sterility
- residual toxicity
- potency and identity
- pH value
- airtightness
- thiomersal
- formaldehyde
- bacterial endotoxins
- viscosity

F. Batch to batch consistency

The consistency of production has been demonstrated and the results of 3 consecutive runs, conforming to the specifications, are provided.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances (inactivated antigens 6 months and bulk of the vaccine 1 month before filling) when stored under the approved conditions (2-8° C).

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 (2-8° C).

The in-use shelf-life of the broached vaccine (10 hours) is supported by the data provided.

H. Other Information

Not applicable.

III. SAFETY ASSESSMENT

The vaccine is recommended for pigs from the age of 6 weeks for 2 doses intramuscular administration at an interval of 3 weeks.

Safety studies have been performed with a vaccine batch with maximum antigen content produced according the described production process.

Field studies have been performed with a representative vaccine batch produced according the described production process.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal is demonstrated in controlled laboratory studies which included 20 vaccinates animals (6-week-old pigs) in total. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

The safety studies demonstrate that the administration of one dose, an overdose and the repeated administration of a dose can be considered to be safe, when used in accordance with the recommended vaccination schedule. Some minor, transient adverse reactions were observed following vaccination. Appropriate warning regarding local site reactions following vaccination have been included in the SPC: Common local reactions (reddish swelling, induration) can occur with a diameter of 10 cm after the administration of the determined dose, which spontaneously subside within 3 to 14 days. Temporary elevation of body temperature by 1.0 °C could occur in vaccinated animals commonly.

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for pregnant animals.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study was not carried out.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

Antigens are inactivated by formaldehyde, further it contains a lipid solvent as immunity adjuvant and thiomersal as a preservative agent. Thiomersal and formaldehyde do not represent any significant risk to consumers. They are included in the List of Allowed Pharmacologically active substances in Annex to the COMMISSION REGULATION (EU) No 37/2010 without maximum residue limit. Thiomersal does not need to be determined in multiple-dose vaccines where thiomersal is used as a preservative in concentrations not exceeding 0.02%.

According Ph. Eur., where formaldehyde has been used in the preparation, the concentration of free formaldehyde is not greater than 0.5 g/l, unless a higher amount has been shown as safe. Amount of 1 mg/ml used in vaccine SMATRVAC APP 2,9,11 was shown as safe in safety study.

For this reason, testing of residues in tissues after application of SMARTVAC APP 2,9,11 was not performed. 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

Combined safety and efficacy field trial was performed on target animals.

30 piglets 6 weeks old were always used in three farms. Twenty piglets were vaccinated by the tested vaccine with the average antigen content according to the recommended vaccination scheme, ten piglets were held as the non-vaccinated control. Body temperature, clinical symptoms as shortness of breath, cough, vomiting or death in pigs was recorded regularly. At the end of fattening the animals were slaughtered and the pulmonary scope was determined in each pig in conformity with Ph. Eur. requirements, the level of antibodies against *A. pleuropneumoniae* was determined in the blood serum and re-isolation of *A. pleuropneumoniae* from the taken sample of the pulmonary tissue, tracheobronchial lymph nodes and tonsils.

The results of field studies are in compliance with Ph. Eur. Monograph 1360, no animal showed notable signs of disease or died from causes attributable to the vaccine; the average body temperature increase for all animals did not exceed 1.5 °C; and no animal showed a rise in body temperature greater than 2 °C.

The results from field trials reflect those observed in laboratory trials.

Environmental Risk Assessment

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

The assessment concluded that there is a negligible risk to the environment associated with use of the vaccine. 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. CLINICAL ASSESSMENT (EFFICACY)

All trials performed to demonstrate efficacy of SMARTVAC APP 2,9,11 vaccine were designed to comply with the requirements of relevant European veterinary legislation including the European Directive 2001/82/EC as amended and relevant European Pharmacopoeia chapters in force. The efficacy of the product has been demonstrated in laboratory challenge studies in accordance with the Ph. Eur. monograph 1360: Porcine actinobacillosis vaccine (inactivated).

For verify the efficacy of developed vaccine in target animals were used two batches:

batch with the minimum antigen content proposed for common production batches and batch with 50% of antigen content against the consider minimum antigen content.

To induce experimental infection (challenge) *Actinobacillus pleuropneumoniae* s. 2 and s. 9 virulent strains of a different origin from the vaccine strain were used, producing relevant APX toxins (APX I, II and APX II, III). All three ApX groups are represented in the vaccine. The significance of toxigenic group is supported by the specific monograph 1360 which states (Section 2.2.2 Immunogenicity) that "The challenge strain for the following test is chosen to ensure challenge with each Ap toxin produced by the serotypes to be stated on the label...". In view of the fact that serotypes 9 and 11 belong to the same toxigenic group (Group 1, producing ApX I and ApX II) and Serotype 2 belongs to toxigenic group 2, producing ApX II and

ApX III, then this Ph. Eur. requirement could be considered met by challenge studies with serotype 2 and 9.

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that the vaccine reduces lung lesions and colonisation of the respiratory tract by *Actinobacillus pleuropneumoniae*.

The laboratory efficacy study included the following evaluation:

Onset of immunity

Forty-two piglets aged 6 weeks, without antibodies against antigens in the vaccine, were used.

14 piglets were vaccinated with the test vaccine with the minimum antigen content according to the recommended vaccination schedule, 14 piglets were vaccinated with the test vaccine with 50% of the minimum antigen content and 14 piglets were kept as unvaccinated controls. Twenty-one days after revaccination always 7 piglets of each group received one of two challenge strains of *A. pleuropneumoniae*: serotype 2, producing APX II and III, and serotype 9, producing APX I and II. Clinical symptoms of the disease (dyspnoea, cough, vomiting, anorexia, lethargy), or death were regularly recorded after challenge. The animals were slaughtered at the end of 7-day observation period and lung scores were determined according to the Pharm. Eur. requirements. *A. pleuropneumoniae* was re-isolated from lung tissue, tracheobronchial lymph nodes and tonsils.

Both potency variants of the test vaccine (i.e. with the lowest antigen content considered for the vaccine production and with the 50% content of this minimal variant) met the efficacy parameters required by Pharm. Eur. monograph 1360 "Vaccinum actinobacillosis inactivatum ad suem". It was proved that the SMARTVAC APP 2,9,11 vaccine was able to reduce significantly typical lung lesions of the disease and to reduce infection three weeks after revaccination according to the proposed vaccination schedule.

Duration of immunity

Twenty-eight piglets aged 6 weeks, without antibodies against antigens included in the vaccine, were used.

Blood samples were taken before vaccination and then regularly at weekly intervals until 21 days after revaccination to determine levels of antibodies against vaccine antigens; additional sampling was performed before the experimental infection, i.e. 20 weeks after revaccination.

Fourteen piglets were vaccinated with the test vaccine with the minimum antigen content according to the recommended vaccination schedule and 14 piglets were kept as unvaccinated controls. Twenty weeks after revaccination always 7 piglets of each group received one of two challenge strains of *A. pleuropneumoniae* (producing either APX I and II or APX II and III). Clinical symptoms of the disease (dyspnoea, cough, vomiting, anorexia, lethargy), or death were regularly recorded after challenge. The animals were slaughtered at the end of 7-day observation period and lung scores were determined according to the Pharm. Eur. requirements and *A. pleuropneumoniae* was re-isolated from lung tissue, tracheobronchial lymph nodes and tonsils.

The duration of active immunity was verified successfully by challenge test 20 weeks after revaccination, i.e. in the time covering reliably the fattening period. The duration of immunity was also supported by the persisting antibody level against individual vaccine antigens.

The levels of antibodies against individual vaccine antigens at the end of the expected duration of immunity agreed with the quantities of antibodies which were verified as protective in the subminimum vaccine batch (i.e. with 50% antigen content) in the test of the onset of immunity.

The following claimed indications for SMARTVAC APP 2,9,11 are considered to be supported by the laboratory studies:

For active immunisation of fattening pigs from 6 weeks of age onwards to reduce lung lesions and to reduce colonisation of the respiratory tract by Actinobacillus pleuropneumoniae – the causative agent of pleuropneumonia in pigs.

Onset of immunity: 3 weeks after complete vaccination

Duration of immunity: 20 weeks after complete vaccination

Influence of Maternal antibodies on efficacy

Twenty-eight piglets aged 6 weeks, born from mothers vaccinated with the antigens contained in the test vaccine were used - the sows were vaccinated with a vaccine batch with an average content of antigens 6 weeks and 3 weeks before parturition, always with a dose of 1 ml i.m.

Blood samples were taken before the vaccination of piglets and then regularly at weekly intervals until experimental infection to determine levels of antibodies against vaccine antigens.

Fourteen piglets were vaccinated with the test vaccine with the minimum antigen content according to the recommended vaccination schedule and 14 piglets were kept as unvaccinated controls. Twenty-one days after revaccination always 7 piglets of each group received one of two challenge strains of *A. pleuropneumoniae* (producing either APX I and II or APX II and III).

Clinical symptoms of the disease (dyspnoea, cough, vomiting, anorexia, lethargy), or death were regularly recorded after challenge. The animals were slaughtered at the end of 7-day observation period and lung scores were determined according to the Pharm. Eur. requirements and *A. pleuropneumoniae* was re-isolated from lung tissue, tracheobronchial lymph nodes and tonsils.

The presence of maternally derived antibodies in piglets at the age of 6 weeks does not influence the efficacy of the vaccination and the onset of active immunity 21 days after the revaccination.

Field Trials

Combined safety and efficacy field trial was performed on target animals.

In total 60 piglets from 3 farms, vaccinated at the age of 6 weeks, were used for verification of efficiency of the tested medicinal product. Piglets were examined for presence of the antibodies against *A. pleuropneumoniae* s.2, s.9, s.11 and APX toxins. In each farm twenty piglets were vaccinated by the tested vaccine with the average antigen content according to the recommended vaccination scheme, ten piglets were held as the non-vaccinated control. Before vaccination, before revaccination and 21 days after revaccination blood samples were collected for determination of the level of antibodies against antigens in vaccine; additional sampling was conducted at the end of fattening.

By the end of fattening the animals were slaughtered and the pulmonary score was determined in each pig in conformity with Pharm. Eur. requirements, the level of antibodies against *A. pleuropneumoniae* was determined in the blood serum and re-isolation of *A. pleuropneumoniae* from the taken sample of the pulmonary tissue, tracheobronchial lymph nodes and tonsils.

Clinical symptoms as shortness of breath, coughing, vomiting or death in pigs were recorded regularly.

The results obtained in this study confirm laboratory trials findings. Administration of the vaccine at the recommended dose and by the recommended route of administration proved to be safe and effective for the target species. Significant increase of antibodies

level was proved in all vaccinated animals. Suitable level of antibodies persisted for the fattening period.

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

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.

Administrative changes

Summary of change (Application number)	Section updated in Module 3	Approval date
RMS change from CZ/V/0158/001 to NL/V/0430/001	Admin. info	01/03/2024