Institute for State Control of Veterinary Biologicals and Medicines
Hudcova 56a
621 00 Brno
Czech Republic
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

FIXR M Hyo One emulsion for injection for pigs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	CZ/V/0161/001/DC
Name, strength and pharmaceutical form	FIXR M Hyo One emulsion for injection for pigs
Applicant	Kernfarm B.V., De Corridor 14D, 3621 ZB Breukelen, The Netherlands
Active substance(s)	Inactivated *Mycoplasma hyopneumoniae* strain 1137
ATC Vetcode	QI09AB13
Target species	Pigs (fattening pigs)
Indication for use	For active immunization of fattening pigs from 7 days of age to reduce lung lesions caused by *Mycoplasma hyopneumoniae* - a causative agent of enzootic pneumonia in pigs. Onset of immunity: 14 days after administration of a single dose. In farms with high infection pressure by *Mycoplasma hyopneumoniae* where 2 doses with an interval of 3 weeks can be administered: 14 days after completion of the vaccination scheme. Duration of immunity: 26 weeks after vaccination with a single dose. In farms with high infection pressure by *Mycoplasma hyopneumoniae* where 2 doses with an interval of 3 weeks can be administered: 26 weeks after completion of the vaccination scheme.

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	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original <mutual recognition> <decentralised>procedure	26/09/2019
Date product first authorised in the Reference Member State (MRP only)	NA
Concerned Member States for original procedure	RMS: CZ CMS: BE, NL

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

One vaccine dose (2 ml) contains:

Active substance:
Inactivated *Mycoplasma hyopneumoniae* strain 1137 RP ≥ 1*

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

Adjuvant:
Oil emulsion Montanide ISA 35 VG 0.2 ml

Excipients:
Formaldehyde max. 2 mg
Thiomersal 0.2 mg
Sodium chloride
Water for injection

The vaccine is presented in:

Glass injection vials of hydrolytic class I:	10-ml vial containing 10 ml
Glass injection vials of hydrolytic class II:	100-ml vial containing 100 ml
Plastic injection vials HDPE:	15-ml vial containing 10 ml
	120-ml vial containing 100 ml
Plastic bottles HDPE:	250-ml bottle containing 250 ml

The vials or bottles are hermetically closed with chlorobutyl rubber stopper and sealed with aluminium cap and are packed in a cardboard box.
Multiple packed vials are placed in a cardboard box or a plastic box with wells.
Pack sizes: 10 x 5 doses (10 x 10 ml), 1 x 50 doses (1 x 100 ml), 1 x 125 doses (1 x 250 ml)

The particulars of the containers and controls performed are provided and conform to the regulation of monographs 3.2.1, 3.2.2 and 3.2.9 of the European Pharmacopoeia.

The choice of the vaccine strain, of the vaccine composition, adjuvant, inactivating agent, preservative and of the content of antigen 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 substance is inactivated *Mycoplasma hyopneumoniae* which is established active substance. The active substance is 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, optical control of growth, strain identity control, density control, pH control, inactivation control, pH control of inactivated bacterin, quantification of inactivated bacterin prior to homogenization, 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
- live mycoplasma
- potency and identity
- pH value
- airtightness
- thiomersal
- formaldehyde
- 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 substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance (inactivated antigen 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 piglets from 7 days of age for 2 doses intramuscular administration at an interval of 3 weeks or for piglets from 11 days of age for 1 dose intramuscular administration. Selection of the vaccination scheme depends on knowing the disease incidence on a particular farm.

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 and repeated dose and an overdose in the target animal is demonstrated in controlled laboratory studies which included 20 vaccinates piglets at the age of 7 days 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 and repeated dose and an overdose 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 up to 3 cm in diameter can occur after application, which disappear spontaneously within 3 days. Very commonly animals may manifest a transient increase in body temperature max. 1 °C.

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 lipoid 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 this vaccine was shown as safe in safety study.

For this reason, testing of residues in tissues after application of this vaccine 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.

Field studies were performed on three farms. Piglets were vaccinated by the tested vaccine batch with the average antigen content according to the recommended vaccination scheme. For verification of safety of a single and the repeated dose the animals, vaccinated within the scope of the test for efficiency of the medicinal product in the one-dose and the two-dose vaccination scheme, were used. 20 pieces of piglets and 10 controls were used on each farm for each vaccination scheme.

The vaccinated animals were monitored for presence of possible local or overall reactions. Body temperature in the vaccinated as well as in the control animals was recorded.

The results of field studies are in compliance with Ph. Eur. Monograph 2448, 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 FIXR M Hyo One 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 piglets in accordance with the Ph. Eur. monograph 2448: Porcine enzootic pneumonia vaccine (inactivated)

Efficacy studies have been performed with two vaccine batches with minimum antigen content produced according the described production process and with one batch with 10% of the minimum antigen content.

One batch with minimal antigen content was used to verify OOI 21 days after vaccination and the other batch was additionally used to determine OOI 14 days after vaccination.

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

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 caused by *Mycoplasma hyopneumoniae* - a causative agent of enzootic pneumonia in pigs.

The laboratory efficacy study included the following evaluation:

1. One-dose application: Vaccination at 11 days of age
   - 1.1. Onset of immunity in 21 days
   - 1.2. Onset of immunity in 14 days
   - 1.3. Duration of immunity
   - 1.4. Influence of colostral immunity on the efficacy
   - 1.5. Influence of MDA on onset of immunity
   - 1.6. Influence of MDA on duration of immunity
2. Two-dose application: Primary vaccination at 7 days of age, revaccination 3 weeks later
   - 2.1. Onset of immunity in 21 days
   - 2.2. Onset of immunity in 14 days
   - 2.3. Duration of immunity
   - 2.4. Influence of colostral immunity on the efficacy
   - 2.5. Influence of MDA on onset of immunity
   - 2.6. Influence of MDA on duration of immunity

Onset of immunity

Efficacy was assessed by comparing lung lesion scores following challenge in groups of vaccinated and non-vaccinated piglets according to the Ph. Eur. requirements.

For each challenge test twelve vaccinated piglets and eight non-vaccinated piglets were used. Piglets were vaccinated with the test vaccine with the minimum antigen content (or with 10% antigen content) according to the recommended vaccination schedules. Challenge tests of efficacy were performed in laboratory conditions 21 days and additionally 14 days after immunization. The animals were killed 30 days after infection and their lung scores were determined according to the Ph. Eur. requirements and samples of affected lung tissue were taken to determine the presence of *M. hyopneumoniae*.

Both potency variants of the test vaccine (i.e. with the lowest antigen content considered for the vaccine production and with the 10% content of this minimal variant) met the efficacy parameters required by Ph. Eur. monograph 2448: Porcine enzootic pneumonia vaccine (inactivated).

Within the verification of the onset of immunity after one-dose administration of the test item at the age of 11 days and two-dose application at 7 days of age with revaccination 3 weeks later, a significantly lower incidence of typical pulmonary lesions was recorded after challenge in the animals vaccinated as compared with the control group of unvaccinated

animals. The onset of active immunity was demonstrated in 21 days and 14 days after vaccination.

It was proved that the FIXR M Hyo One vaccine was able to reduce significantly typical lung lesions of the disease according to the proposed vaccination schedule.

Duration of immunity

The duration of immunity in piglets has been shown by challenge trial.

Efficacy was assessed by comparing lung lesion scores following challenge in groups of vaccinated and non-vaccinated piglets according to the Ph. Eur. requirements.

The study design was the same as in the study for onset of immunity. Twelve vaccinated piglets and eight non-vaccinated piglets were used. Piglets were vaccinated with the test vaccine with the minimum antigen content according to the recommended vaccination schedules. Challenges were performed 26 weeks after vaccination. The animals were killed 30 days after infection and their lung scores were determined according to the Ph. Eur. requirements and samples of affected lung tissue were taken to determine the presence of *M. hyopneumoniae*.

Within the verification of the duration of immunity after one-dose administration and two-dose application, a significantly lower incidence of typical pulmonary lesions was recorded after challenge in the animals vaccinated as compared with the control group of unvaccinated animals. The presented data demonstrate that active immunity persists for at least 26 weeks after vaccination.

The following claimed indications for FIXR M Hyo One are considered to be supported by the laboratory studies:

For active immunization of fattening pigs from 7 days of age to reduce lung lesions caused by Mycoplasma hyopneumoniae - a causative agent of enzootic pneumonia in pigs.

Onset of immunity: 14 days after administration of a single dose.
In farms with high infection pressure by Mycoplasma hyopneumoniae where 2 doses with an interval of 3 weeks can be administered: 14 days after completion of the vaccination scheme.

Duration of immunity: 26 weeks after vaccination with a single dose.
In farms with high infection pressure by Mycoplasma hyopneumoniae where 2 doses with an interval of 3 weeks can be administered: 26 weeks after completion of the vaccination scheme.

Influence of Maternal antibodies on efficacy

Studies “Influence of colostral immunity on the efficacy” (challenge 21 days after vaccination) were not conducted in accordance with the instruction EMA/CVMP/IWP/439467/2007.

The new studies were carried out by the applicant relating to demonstration of MDA influence

- on the onset of immunity in a 1-dose and 2-dose vaccination schedule
- and on duration of immunity in a 1-dose and 2-dose vaccination schedule.

The presence of maternally derived antibodies against *Mycoplasma hyopneumoniae* in piglets at the age of 11 days does not influence the efficacy of the 1-dose vaccination as well as at the age of 7 days does not influence the efficacy of the 2-dose vaccination.

The onset of active immunity 14 days after the application of the vaccine and the duration of active immunity 26 weeks after the application were also demonstrated in the presence of MDA.

The study meets the requirements of EMA/CVMP/IWP/439467/2007 Reflection paper on the demonstration of a possible impact of maternally derived antibodies on vaccine efficacy in young animals. The extent of the lung lesions was evaluated according to Ph. Eur. monograph 2448 ´Vaccinum pneumoniae enzooticae suillae inactivatum´.

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 11 days, were used for verification of efficiency of the vaccine in a common vaccination dose (1-dose vaccination scheme). Further 30 piglets serve as the non-vaccinated control group.

In total 60 piglets from 3 farms, vaccinated at the age of 7 days, were used for verification of efficiency of the vaccine in a common vaccination dose (2-dose vaccination scheme). Further 30 piglets serve as the non-vaccinated control group.

Assessment of efficiency was realized by evaluation of the pulmonary score in conformity with requirements of Ph.Eur. and by comparison of this score in vaccinated animals and the non-vaccinated control group.

The level of antibodies against *Mycoplasma hyopneumoniae* in vaccinated and control animals was determined and re-isolation of this pathogen from the pulmonary tissue was carried out as the proof of exposure to natural infection.

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.

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 Vetrinary 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.

None