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"MUTUAL RECOGNITION DECENTRALISED" PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

26/07/2019

"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 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0278/001/DC
Name, strength and pharmaceutical form	Hyogen emulsion for injection for pigs
Applicant	CEVA SANTE ANIMALE
Active substance(s)	*Mycoplasma hyopneumoniae*, strain 2940
ATC Vetcode	QI09AB13
Target species	Pigs for fattening
Indication for use	Active immunisation of fattening pigs from 3 weeks of age to reduce the occurrence and severity of lung lesions caused by *Mycoplasma hyopneumoniae* infection Onset of immunity: 3 weeks after vaccination Duration of immunity: 26 weeks after vaccination

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	New active substance, application in accordance with Article 32(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25/03/2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, HR, HU, IE, IT, LT, LV, NL, PL, PT, RO, SE, SI, SK, UK

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. Composition

One dose (2 ml) of the product contains:

Active substance:
Inactivated *Mycoplasma hyopneumoniae* 2940 strain: min. 5.5 EU *

* Mean antibody titre – expressed in *M. hyopneumoniae* ELISA Unit – obtained 28 days after the immunisation of rabbits with half of pig vaccine dose (1ml).

Adjuvants:

Light liquid paraffin	187 µl
Escherichia coli J5 LPS	1184-38000 Endotoxin unit

Excipients:

Thiomersal 50 µg

Sorbitan trioleate, polysorbate 80, sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate, water for injection

The container/closure system consists of low density polyethylene bottle of 50, 100 or 250 ml volume, sealed with rubber stopper and aluminium. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the complex adjuvant (mineral oil associated with *Escherichia coli* J5 LPS), the vaccine strain *Mycoplasma hyopneumoniae* 2940, the formulation, the inactivating agent (ethylene-imine), the preservative (thiomersal) are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

The product is an established pharmaceutical form.

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.

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

C. Control of Starting Materials

The active substance is *Mycoplasma hyopneumoniae strain 2940*, a novel active substance. The active substance is manufactured in accordance with

the principles of good manufacturing practice. The origin of and the tests performed on the *Escherichia coli* J5 LPS used as a component of the adjuvant are correctly documented.

Starting materials of non-biological origin used in production comply with 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.; 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.

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 conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular appearance, filling volume, viscosity, sterility, type and stability of emulsion, thiomersal content, bacterial endotoxin content, potency and identification of the active ingredient.
The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
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 when stored under the approved conditions.

The in-use shelf-life of the broached vaccine is supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

None.

III. SAFETY ASSESSMENT

The studies required by the regulation were performed with batches of standard formulation, completed by a specific assessment of the safety of the adjuvant with experimental batches of specific formulation.

Laboratory trials

The safety in the target animal is demonstrated in 2 laboratory studies involving overall 45 vaccinated pigs and 24 controls. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended, the relevant guidelines and the Ph. Eur. monograph 2448 “porcine enzootic pneumonia vaccine (inactivated)”; this investigation also included a closer examination of the post-vaccination hyperthermia, with additional body temperature records 2 and 6 hours after injection, because of the particular adjuvant of this vaccine. The SPC describes the adverse reactions observed. An additional study investigated more specifically the effect of the adjuvant using experimental batches not representative of standard production.

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

The adjuvant and excipients used are light liquid paraffin, sorbitan trioleate, polysorbate 80, *Escherichia coli* J5 LPS, thiomersal (less than 0.02% in the final product), sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate, water for injection. Based on this information and MRL regulation, 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

3 field studies were performed involving more than 600 pigs from 2 different farms, half of them being vaccinated and half being controls. A closer monitoring for safety involved 28 vaccinates and 28 controls in each of the studies. The results were consistent between the trials and with the laboratory data.

Ecotoxicity

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 no warnings are required.

This is a vaccine containing an oil adjuvant which may induce severe local reaction if self-injected. The appropriate warning for the user is included in the SPC.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.B Clinical Studies

Laboratory Trials

The claimed indications are supported by laboratory studies in piglets vaccinated according to the claims (aged 21 - 25 days at vaccination, single dose of 2ml by IM route in the neck); the challenge was performed by intranasal application of a heterologous *Mycoplasma hyopneumoniae* challenge strain by intranasal route. After challenge, the animals were observed for clinical signs and lung lesions at slaughter 4 weeks later, scoring the lesions in accordance with Ph. Eur.
monograph 2448 'porcine enzootic pneumonia vaccine (inactivated)'. A group of unvaccinated pigs was included in all the trials; the efficacy is expressed in reference to this group.

A first trial involved 5 groups of 12 seronegative pigs – different formulations tested (study on the minimum protective dose). Statistically significant reduction of lung lesions score (LLS) was observed at standard formulation (and also for some reduced formulations), after a challenge 21 days after vaccination. A 2nd study involved 3 groups of 16 pigs of different serological status at time of vaccination (study on the impact of maternally derived antibodies MDA).
Statistically significant reduction of LLS was observed for the 2 vaccinated groups challenged 16 days after vaccination. However the number of seropositive pigs was too low to draw a clear conclusion on the impact of MDA on vaccine uptake. It was not possible to exclude a possible interference of the MDA with the vaccine uptake justifying the following warning in the SPC section 4.9 Amounts to be administered and administration route "The data

available are not sufficient to exclude the interaction of maternally derived antibodies with vaccine uptake. Interaction with maternal-derived antibodies is known and should be taken into consideration. It is recommended to delay vaccination in piglets with residual MDA at the age of 3 weeks."
A 3rd study involved 2 groups of 15 seronegative piglets (study to support the shelf-life). Statistically significant reduction of LLS was observed for the vaccinates challenged 21 days after vaccination.
A 4th study involved 3 groups of 15 seronegative piglets (study to support the effect of LPS). Statistically significant reduction of lung lesions score (LLS) was observed for the vaccinates receiving the standard vaccine challenged 18 days after vaccination.
These studies support an onset of immunity of 3 weeks and the claim of reduction of the occurrence and severity of lung lesions caused by *Mycoplasma hyopneumoniae* infection.

The duration of immunity of 6 months was supported by challenges performed 6 months after vaccination in 3 different trials.
In two laboratory studies involving a total of 3 groups of 20 seronegative pigs, a statistically significant reduction of LLS was observed for the 2 vaccinated groups, one receiving a standard batch and one a sub-formulated batch of vaccine.
In a third study involving 20 pigs vaccinated in a farm and their control mates, both challenged under laboratory conditions, a statistically significant reduction of LLS was observed for the vaccinates.

The effect on clinical signs, mycoplasma re-isolation from lungs and weight gain were also studied but the results were not consistent enough to support these claims.

Field Trials

The applicant has conducted 2 field studies in 2012; one study was inconclusive. The other study involved 230 vaccinated and 230 control animals and showed a significant reduction of the incidence of pleurisy, lung lesions at slaughter and morbidity rate in vaccinates.

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 veterinary Heads of Agencies website (http://mri.medagencies.org/veterinary/).

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.

Quality changes

Summary of change	Approval date
IB003 - Addition of an alternate QC site for Ceva-Phylaxia (animal phase of batch potency test)	2016
II002G - Change in physico-chemical specifications of the final product	2016
II009 – addition of a vial size (200 ml)	2019
II008 – improvement of the quantification and change of final specifications for the J5 component (adjuvant)	2019
IB010 – Removal of J5 control test during stability test of the finished product	2019