ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Suvaxyn M.hyo- Parasuis, Suspension for Injection for Pigs

PuAR correct as of 09/03/2018 when RMS was transferred to DE. Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0279/001/MR
Name, strength and pharmaceutical form	Suvaxyn M. hyo - Parasuis, suspension for injection for pigs Inactivated *Mycoplasma hyopneumoniae*, strain P-5722-3 Inactivated *Haemophilus parasuis* serotype 4, strain 2170B Inactivated *Haemophilus parasuis* serotype 5, strain IA84-29755 * Relative potency as compared to a reference in an in-vitro ELISA assay
Applicant	Zoetis UK Limited 5th Floor, 6 St. Andrew Street London EC4A 3AE
Active substances	Inactivated *Mycoplasma hyopneumoniae* Inactivated *Haemophilus parasuis* serotype 4 Inactivated *Haemophilus parasuis* serotype 5
ATC Vetcode	QI09AB17
Target species	Pigs (fatteners)
Indication for use	For the active immunisation of pigs to reduce lung lesions caused by *Mycoplasma hyopneumoniae* and to reduce lesions and clinical signs caused by *Haemophilus parasuis* serotypes 4 and 5. Onset of immunity against *Mycoplasma hyopneumoniae* has been demonstrated one week after second vaccination. Onset of immunity against *Haemophilus parasuis* serotype 4 and 5 has been demonstrated 3.5 weeks after second vaccination. Duration of immunity studies indicate that the vaccine protects for 6 months after the second vaccination against *Mycoplasma hyopneumoniae* and *Haemophilus parasuis* serotypes 4 and 5.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual recognition application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	27 February 2008
Date product first authorised in the Reference Member State (MRP only)	21 March 2006
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark. Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain

I. SCIENTIFIC OVERVIEW

The product is for use in pigs, to reduce lung lesions caused by *Mycoplasma hyopneumoniae* and to reduce lesions and clinical signs caused by *Haemophilus parasuis* serotypes 4 and 5. A 2 ml dose is administered via intramuscular injection to the neck, pigs can be vaccinated from the age of 7 days. A second vaccination is performed 14-21 days after the first.

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

The product contains inactivated *Mycoplasma hyopneumoniae*, inactivated *Haemophilus parasuis* serotype 4, inactivated *Haemophilus parasuis* serotype 5 and excipients thiomersal, amaranth, ethylenediaminetetraacetic acid, sodium chloride, sodium phosphate dibasic and water for injections.

The container/closure system comprises high density polyethylene (HDPE) vials with chlorbutyl rubber stoppers and aluminium caps consisting of a 25 ml volume vial containing 10 doses, a 60 ml volume vial containing 25 doses, a 120 ml volume vial containing 50 doses or a 250 ml volume vial containing 125 doses. Packaging consists of a cardboard box with 1 or 10 HDPE vials of 25, 60, 120 or 250 ml. Additionally there is a low density polyethylene (LDPE) sachet of 100 ml contain 50 doses, the packaging for which is a cardboard box with 1 or 10 LPDE sachets. The particulars of the containers and controls performed are provided and conform to the regulation. There is no pharmacopoeial monograph for the aluminium overseals which are used to secure the chlorbutyl stoppers, as this material does not come into contact with the product.

The choice of the vaccine strain, inactivating agents, presence of preservative 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.
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances are inactivated *Mycoplasma hyopneumoniae*, inactivated *Haemophilus parasuis* serotype 4, inactivated *Haemophilus parasuis* serotype 5, established active substances. The active substances comply with in-house specifications.

Other ingredients comply with the relevant pharmacopoeial monographs where these exist. In other cases, the company has identified the source of each ingredient, explained how its quality is controlled and provided relevant certificates of analysis.

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 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 general characteristics, assay, potency, safety tests, sterility and purity, inactivation, residual moisture and batch to batch consistency. 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. 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.

No data are available on the stability of the product once the container has been started, and the summary of product characteristics therefore contains an instruction to use the contents of a broached container immediately.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life:
2 years as packaged for sale.
Shelf-life after first opening: Use immediately.

Special precautions for storage:
Store and transport refrigerated at 2°C – 8°C.
Store protected from light in the original container.
Do not freeze.

III. SAFETY ASSESSMENT

Laboratory trials

The effect of a single dose, an overdose and a repeated single dose of the vaccine was investigated. The vaccine administered in this study included the maximum allowable amount of bacteria and an excess of Carbopol, to represent a worst case situation. The piglets ranged from 6 – 10 days of age.

Some of the piglets which received a single dose (2 ml) of the vaccine experienced a fever soon after vaccination but this had gone within 24 hours. Some also had a mild swelling at the site of the injection but this had gone within 3 – 4 days. Microscopic examination of the injection site fourteen days after vaccination revealed evidence of mild inflammation in some piglets, but no more serious reactions.

Piglets which received the overdose (4 ml instead of 2 ml) had similar reactions to those which received 2 ml, but in some cases the injection site reactions persisted for longer (up to ten days).

In the repeated dose part of the study, the piglets received a 2 ml dose followed by second 2 ml dose 14 days later, and a third dose 14 days after that. Injections were given on alternate sides of the neck. Effects after the first and second injections were similar to those observed in the single-dose part of the study. However, after the third injection, the reactions at the injection site were rather larger and persisted for slightly longer (up to 8 days).

The pivotal study described above was supplemented by the reports of two other studies in which similar effects were observed.

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.

There is no residue risk with this vaccine and 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

Three field studies have been conducted. In the first two studies, the farms in question were suffering from infections with *M. hyopneumoniae* and *H. parasuis.* In one study, piglets were vaccinated at 5 – 7 days of age and again 11 – 14 days later and in the other study, they were vaccinated at 3 – 10 days and again 2 – 3 weeks later. In the first study, the only sign noted in vaccinated piglets was slight swelling at the injection site in some animals. Similar signs were observed in the second study, but in this case, some nervous signs were also seen. The data from these pivotal studies were supported by data from another field trial in which similar effects were again observed.

A further field study showed that apart from one pig, the reaction to the vaccinations, on the farms, were mild and transient. This supports safety of the product in young pigs, under field conditions.

Ecotoxicity

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

is required. 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)

Clinical Studies

Laboratory Trials

A series of studies was conducted in piglets without maternal antibodies to *M. hyopneumoniae* or *H. parasuis* to identify how long it takes for immunity to develop following vaccination. In each study the piglets received a first dose of vaccine by intramuscular injection at the age of 7 – 10 days, followed by a second dose 14 days later. Vaccinated piglets were exposed to virulent *M. hyopneumoniae* one week after the second injection, or to virulent *H. parasuis* approximately three and a half weeks after the second injection.

In the case of *M. hyopneumoniae*, the effects of vaccination with Suvaxyn M hyo - Parasuis were compared with the effects of vaccination with a vaccine containing only *M. hyopneumoniae*. The major criterion for success was a reduction in the incidence and extent of damage to the lungs, evident at post mortem. Such damage was significantly reduced in vaccinated piglets compared with unvaccinated ones. The results were very similar for both vaccines, and this showed that there was no adverse effect on the efficacy of the *M. hyopneumoniae* component of the vaccine as a result of being combined with *H. parasuis.*

In the case of *H. parasuis*, the virulent bacteria to which the piglets were exposed were of several different serotypes. As well as serotypes 4 and 5, serotypes 2, 12, 13 and 14 were also tested. Clinical signs of disease and mortality were significantly reduced when vaccinated piglets were exposed to serotypes 4 and 5, compared with unvaccinated piglets. There was also a significant reduction in the number of piglets from which virulent bacteria were excreted and in the incidence of post mortem findings. The vaccinated piglets also showed some evidence of being protected from disease caused by serotypes 13 and 14, but they were not protected from disease caused by serotypes 2 and 12. The vaccine used in some of the piglets contained a higher than normal amount of *M. hyopneumoniae* in order to check that efficacy against *H. parasuis* was not adversely affected by the presence of *M. hyopneumoniae*.

Studies were also carried out to investigate how long the immunity to each vaccine component lasted. In these studies, vaccinated piglets were exposed to virulent *M. hyopneumoniae* or *H. parasuis* serotypes 4 or 5, several months later. The results showed that the piglets were protected from disease caused by these bacteria for at least six months.

Further studies aimed to find out if the presence of maternal antibodies had an adverse effect on the efficacy of the vaccine. In one such study, piglets born of vaccinated sows were themselves vaccinated at 7 days of age and again 14 days later. Two weeks after the second vaccination, they were exposed to virulent *H. parasuis* serotype 4 or 5. As in the studies described above, in which piglets had no maternal antibodies to *H. parasuis*, mortality and excretion of bacteria were much reduced compared with unvaccinated animals, although the

difference in clinical signs of disease was less marked. At the time when the piglets were exposed to the virulent bacteria, vaccinated piglets had higher levels of antibodies than did unvaccinated ones, showing that the presence of maternal antibodies at the time of vaccination did not prevent the piglets from developing their own antibodies in response to the vaccine.

Field Trials

In one field study, pigs were vaccinated either with Suvaxyn M hyo - Parasuis or with Suvaxyn M hyo. Both vaccinated groups demonstrated significant improvements in growth rate compared with unvaccinated piglets, and they had a lower incidence of, and less severe damage to, the lungs. The pigs which received the M hyo vaccine had lesions associated with Glässer's disease, whereas pigs which received the combined vaccine had no such lesions. Thus the study indicated that vaccination with M hyo - Parasuis provides protection against Glässer's disease as well as respiratory disease in normal farming situations.

In a second study simply compared the effect of M hyo - Parasuis vaccination with M. hyo vaccination, i.e. there were no unvaccinated piglets. The results showed that the combined vaccine was at least effective as the approved vaccine containing only *M. hyopneumoniae* in controlling signs of respiratory disease under field conditions.

Further field studies have also been conducted to evaluate the field levels of maternally derived antibodies (MDA) in young pigs against *H. parasuis* serovars 4 and 5 (HPS 4 and HPS 5). Data provided indicate that the levels of MDA to HPS 4 at 3 and 5 weeks of age were low level and would not affect the induction of protection. The serological results for HPS 4 from several different countries indicate that there is a significant rise in antibody levels between 3 and 5 weeks of age.

A further field study was also conducted comparing the efficacy of Suvaxyn M hyo/HPS and Suvaxyn M hyo. The trial provided confirmatory evidence that challenge had occurred) and that the vaccine induced a response in the face of field MDA levels at 10 days of age. The study also highlights the early point of challenge with HPS, which also serves to support the recommendation for vaccination from 1 week of age. The vaccine is recommended for use in seronegative piglets from 1 week of age and piglets with MDA from 3 weeks of age. Therefore, these data provide some additional support for the appropriateness of this schedule.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.
(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.
(www.gov.uk/check-animal-medicine-licensed)