Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Suiseng Suspension for Injection for Swine

PuAR correct as of 07/02/2018 when RMS was transferred to IE. Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0324/001/E/001
Name, strength and pharmaceutical form	Suiseng Suspension for Injection for Swine
Applicant	Laboratorios Hipra SA Avda La Selva 135 Amer (Girona) 17170 Spain
Active substance(s)	F4ab fimbrial adhesin of *Escherichia coli* ≥ 65%ER_{60} F4ac fimbrial adhesin of *Escherichia coli* ≥ 78% ER_{70} F5 fimbrial adhesin of *Escherichia coli* ≥ 79% ER_{50} F6 fimbrial adhesin of *Escherichia c*oli ≥ 80% ER_{25} LT enterotoxoid of *Escherichia coli* ≥ 55% ER_{70} Toxoid Clostridium perfringens type C ≥ 35% ER_{25} Toxoid *Clostridium novyi* type B ≥ 50% ER_{120} *% ERx: Percentage of immunized rabbits with a X serological EIA response
ATC Vetcode	Q109AB08
Target species	Pigs
Indication for use	**Piglets:** For the passive protection of neonatal piglets by means of the active immunisation of breeding sows and gilts to reduce mortality and clinical signs of neonatal enterotoxicosis, such as diarrhoea caused by enterotoxigenic *Escherichia coli*, which express F4ab (K88ab), F4ac (K88ac), F5 (K99) or F6 (987P) adhesins. The persistence of these antibodies has not been established. For the passive immunisation of neonatal

	piglets against necrotic enteritis by means of the active immunisation of breeding sows and gilts to induce seroneutralising antibodies against the β-toxin of *Clostridium perfringens* type C. The persistence of antibodies has not been established. **Sows and gilts:** For active immunisation of breeding sows and gilts to induce seroneutralizing antibodies against the α-toxin of *Clostridium novyi* type B. The relevance of the seroneutralizing antibodies was not experimentally determined. Antibodies have been detected 3 weeks after vaccination. The persistence of these antibodies has not been established.

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	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	21st October 2015.
Date product first authorised in the Reference Member State (MRP only)	5th November 2009.
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden. Concerned Member State added for mutual recognition procedure: Croatia

I. SCIENTIFIC OVERVIEW

Suiseng Suspension for Injection for Swine is a vaccine intended for use in pigs. Diarrhoea in neonatal pigs is a significant disease in which enterotoxigenic and/ or pathogenic strains of *Escherichia coli* (*E. coli*), and *Clostridium perfringens (Cl. perfringens*) may be observed. A variety of strains are included in this product. Suiseng also contains a toxoid of *Clostridium novyi* type B. The classic disease in swine produced by this bacterium is the sudden death of adult, apparently healthy animals.

E. coli bacterial strains produce enterotoxins and exhibit fimbrial adhesins at the cell surface. Fimbrial adhesins are involved in the attachment of the bacterium to the surface of the intestinal epithelium. *E.coli* labile toxin (LT) is associated with the most severe symptoms of colibacillosis in piglets. Antibodies specific for these antigens are present in the colostrum and are able to bind the adhesins in order to block cell entry and also to bind the toxins in order to neutralise them. The vaccine, (which is for administration to pregnant sows), generates an antibody response to adhesins and toxins which is expressed in the colostrum, thus providing passive immunisation for suckling pigs.

Cl. perfringens type C may cause often lethal necrotic enterotoxaemia in piglets during the first few days of life. Antibodies against the necrotic β-toxin produced by this pathogen can block toxic effects and reduce symptoms. *Cl. novyi* can have implications for sows post-parturition, and this portion of the vaccine is intended to support sows during this vulnerable time.

Suiseng Suspension for Injection for Swine is administered intramuscularly into the neck muscles at a dose of 2 ml per animal. The product may be used during pregnancy, from six weeks before the expected farrowing date.

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 and 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 and the overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains the following active ingredients: F4ab fimbrial adhesin of *E. coli* ≥ 65% ER_{60}, F4ac fimbrial adhesin of *E. coli* ≥ 78% ER_{70}, F5, fimbrial adhesin of *E. coli* ≥ 79% ER_{50}, F6, fimbrial adhesin of *E. coli* ≥ 80% ER_{25}, LT enterotoxoid of *E. coli* ≥ 55% ER_{70}, toxoid *Cl. perfringens* type C ≥ 35% ER_{25}, and toxoid *Cl. Novyi* type B ≥ 50% ER_{120}. Excipients (as adjuvant) are aluminium hydroxide gel and ginseng. Other excipients are benzyl alcohol, simethicone and PBS solution.

The container systems are 20 ml, 50 ml and 100 ml Type 1 colourless glass vials, closed with Type 1 rubber stoppers and aluminium caps, or 20 ml, 50 ml 100 ml and 250 ml PET plastic vials, closed with Type 1 rubber stoppers and aluminium caps. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the adjuvant, vaccine strain and presence of preservative (benzyl alcohol), are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated. The product is a novel 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.

The preparation of the different types of antigen varies, but essentially follows the same processes. Working seed bacteria are reconstituted in sterile water and placed on appropriate agar plates or in appropriate media. Growth is allowed to take place, followed by the seeding of specific colonies. The ensuing inoculum is transferred to a final production culture fermentor, where the supernatant is collected for clarification and subsequent processing for use in the final product.

C. Control of Starting Materials

The active substances are established active substances not described in the European Pharmacopoeia (Ph. Eur). The active substances are manufactured in accordance with the principles of good manufacturing practice. Starting materials of non-biological origin used in production comply with monographs cited in the Ph. Eur and biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines. The materials are appropriately screened for the absence of extraneous agents according to the guidelines and any deviation is adequately justified. The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

The majority of the starting materials (excipients) are monographed in the Ph. Eur, these include the following: agar, benzyl alcohol, ethanol, formaldehyde solution (35%), gelatine, ginseng, glucose, glycerol, hydrochloric acid, potassium chloride, riboflavin, simethicone, sodium chloride, sodium hydroxide and water for injections. Other excipients not monographed in a pharmacopoeia include tryptose/tryptose soy broth, yeast extract, casein amino acids and various tryptones and peptones.

Strains of bacteria were obtained from a variety of sources, the identity of which was confirmed and for which appropriate tests on viability, purity, fungal sterility, haemolysis, titre and genetic analysis were performed.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

The applicant provided a signed TSE declaration, a Format 2 table, an extensive risk assessment and references to certificates of suitability leading to the conclusion that the risk of contamination of the product with TSE agents is minimal.

E. Control Tests during Production

The tests performed during production are described and the results of three 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 and any deviation from these requirements is justified. The tests include in particular data on appearance, residual formaldehyde quantity of the various excipients, volume, bacterial and fungal sterility, pH, endotoxin, and safety and potency.

The demonstration of the batch to batch consistency is based on the results of a series of batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

Real-time stability data, plus additional data, were provided on the storage of the inactivated vaccine bottled in the two specified container types. An acceptable shelf-life of fifteen months was established from these studies.[1]

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in the manufacture of the product. 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 eight to ten hours for the reconstituted vaccine is supported by the data provided.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The shelf-life of the veterinary medicinal product as packaged for sale is eighteen months.[2] Shelf-life after first opening of the immediate packaging is eight to ten hours. The product should be stored at 2ºC to 8ºC, protected from light, and must not be frozen.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal was demonstrated in a variety of studies on the target animal. The trials were performed according to the recommendations of Directive 2001/82/EC as amended and to the relevant guidelines.

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

A series of Good Laboratory Practice (GLP) studies were conducted in the target species. The studies consisted of a vaccination and a challenge phase and were relevant to both the required safety data and to efficacy data. All animals were

[1] Shelf-life changed from fifteen to eighteen months by variation procedure 16th December 2010.
[2] See footnote 1.

confirmed as being seronegative for the antibody of relevance prior to the start of the trials. The first study, a single dose study, tested the safety of the recommended vaccination programme, the serological response in sows and the efficacy of the product in piglets on challenge with an F4ac+F6+ and LT+ *E. coli* strain. This was a randomised, blinded study on an appropriate number of animals, in which safety of the product was confirmed. A placebo was used as a negative control.

The second study was also a single dose study performed in a similar manner to the first. This study analysed the safety of the product in sows and the efficacy of product after challenge of their offspring with F4ab+ and F5+ *E. coli* strain, with a placebo being used as a negative control. Again the product was found to be safe for use in the target species.

A third study addressed the safety for use of the product in pigs challenged with an F4ab+ and F5+ *E.coli* strain. No adverse reactions were seen.

In addition, the applicant submitted further data on a study which analysed the effect of a double dose and a repeated single dose in pregnant sows. No adverse reactions were noted.

Field studies

A field study was conducted to evaluate the safety and efficacy of Suiseng Suspension for Injection for Swine against neonatal piglet diarrhoea. Only safety data is reflected in this part of the report. This was a GLP-compliant, multicentre, randomised, double blind study using a parallel and stratified positive control group with Gletvax 6® as a positive control reference product. The study was performed on four farms in which there had been high incidences of piglet diarrhoea. A suitable number of sows six weeks from parturition were divided into two groups, one group received Suiseng Suspension for Injection for Pigs at 2 ml per sow at days 0 and 21, and the second group received Gletvax 6 ® at 5 ml per sow at days 0 and 28. Blood samples were taken on the day of parturition, and piglets were observed for any adverse reactions over a three week period from birth. Sows were evaluated for reactions to injection up to parturition. No serious adverse reactions were seen in either group.

A second study was performed to evaluate the safety and efficacy of Suiseng Suspension for Injection for Swine against sudden death in sows, caused by *Cl. Novyi.* The study was performed on four farms in which there had been high incidences of sudden death in sows. A suitable number of target animals were treated either with a placebo (2 ml per sow), or with Suiseng Suspension for Injection for Swine (2 ml per sow). No adverse reactions were seen in relation to injections given and no significant differences were observed between treatment groups with regard to general reactions or reproductive parameters.

Residue Studies

No residue studies were required to be performed.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was 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. No residue studies were performed.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

The efficacy of the product was demonstrated in a series of laboratory studies in accordance with the relevant requirements which show that Suiseng Suspension for Injection for Swine is effective in the treatment of neonatal piglet diarrhoea and sudden death in sows with regard to a specified pathogens. Trials were performed as combined safety and efficacy studies, only efficacy data are presented in this section.

Firstly, the applicant provided details of a challenge study of the pathogenicity of a mixed F4ac+ F6+ and LT+ strain of *E.coli*. A suitable number of pregnant sows, free from specific antibodies to target antigens, along with their litters, were included in the trial. A minimum infective dose was determined as cfu/piglet. A second challenge study elucidated the minimum infective dose for an F4ab+ and F5+ strain. These data, which determined the challenge concentration, were used in the following studies.

Subsequent to establishing the minimum infective dose a number of pregnant sows were vaccinated in four GLP-compliant studies with Suiseng Suspension for Injection for Swine, followed by a pre-titred challenge, quantification data for which had been obtained as described above. The immunological protection of sows and subsequently of piglets was supported by the results of these trials. The first study tested the vaccine as being competent against neonatal piglet colibacillosis and clostridial infections. This was a GLP-compliant study performed under randomised and blinded conditions using a vaccination phase and a challenge phase. A suitable number of pregnant sows of appropriate serological status were vaccinated with Suiseng Suspension for Injection for Swine and the ensuing piglets challenged with a mixture of *E.coli* antigens consisting of F4ac, F6 and LT. Results showed that the vaccine was effective against the fimbrial adhesins of strains F4ac+ and F6+ of *E. coli*, and against the enterotoxoid of the LT *E. coli* strain. Piglets were found to be seropositive for the appropriate antibodies.

The second study was performed to GLP under randomised and blinded conditions, again using a vaccination phase and a challenge phase. A number of piglets from specific seronegative, vaccinated gilts and a number of negative control piglets were challenged with *E. coli* F4ab and F5 antigens. Results demonstrated that the vaccine was efficacious against fimbrial adhesins of F4ab and F5 and the LT enterotoxoid. Piglets were shown to be seropositive for the appropriate antibodies. A third study was performed with regard to relevant *Cl.*

perfringens and *Cl. novyi* antigens, and the results contributed to the establishment of the vaccine as being effective as specified in the SPC.

A fourth study observed the efficacy of Suiseng Suspension for Injection for Swine after re-vaccination. The study was performed under randomised and blinded conditions using vaccination and challenge phases. A number of piglets from vaccinated and non-vaccinated sows were challenged with F4ab, F5, F4ac, F6 and LT toxin. Some sows had been re-vaccinated for what would be a second gestation. All animals were established as being of the appropriate immune status. The results contributed to the final evaluation that Suiseng Suspension for Injection for Swine was appropriate for passive immunisation against the pathogenic strains specified in the SPC.

Two potency studies were performed in rabbits in order to establish potency for the Clostridium toxoids used in the vaccine. A first assay was designed to comply with the batch potency test requirements of the corresponding monographs of the European Pharmacopoeia. An appropriate number of rabbits were inoculated with vaccine, blood samples were analysed at days zero, twenty-one and thirty-five and the animals were euthanased after thirty-five days. Results confirmed the potency determination of the Clostridium components of the vaccine. The second study consisted of an analysis of the serological response in rabbits immunised with the swine vaccine. These data supported the use of the vaccine for use in swine.

Field Trials

Two field trials were conducted in order to test the efficacy of the Suiseng vaccine. One trial observed efficacy against relevant *E.coli* and *Cl. Perfringens* antigens, and another trial observed efficacy against *Cl. novyi*. These data were derived from combined safety and efficacy studies. Only data from efficacy studies is presented here. The first study, to analyse efficacy against *E.coli* and *Cl. perfringens* was conducted to GCP as a multicentre, randomised, double blind study using a parallel and stratified control group. A positive control product, Gletvax 6® was used. For Suiseng Suspension for Injection for Swine, a production-level pilot batch were used. An appropriate number of pregnant sows from farms with a high incidence of diarrhoea were administered 2ml of correctly titred Suiseng or Gletvax 6®. The animals and their offspring were observed over a period of time, blood samples being taken from the sows and rectal swabs from the piglets. Serological study supported the employment of Suiseng Suspension Injection for Swine for its intended use as described in the SPC.

The second study GCP was performed in order to analyse the efficacy of the Suiseng vaccine against sudden death in sows caused by *Cl. Novyi*. An appropriate number of sows, selected as described for the previous study, received either correctly titred Suiseng vaccine or a placebo. Observations of the animals were made and the study contributed to the established use of Suiseng Suspension for Injection for Swine for the purpose of treating sudden death in sows.

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)