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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

AviPro THYMOVAC
Lohmann Animal Health GmbH & Co. KG
Heinz-Lohmann Str. 4
27472 Cuxhaven
Germany

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0247/001/MR
Name, strength and pharmaceutical form	**AviPro THYMOVAC** **SE, NO, IS: AviPro® THYMOVAC vet.** 1 dose contains $10^{4.5}$ - $10^{5.5}$ $TCID_{50}$/bird dose live Chicken Anaemia Virus (CAV), strain Cux-1 Lyophilisate for suspension
Applicant	Lohmann Animal Health GmbH & Co. KG Heinz-Lohmann Str. 4 27472 Cuxhaven Germany
Active substances	Live Chicken Anaemia Virus (CAV), strain Cux-1
ATC Vetcode	QI01AD04
Target species	Chickens
Indication for use	For protection of the vaccinated breeder against excretion of the chicken anemia virus and transmission of the virus to eggs. For passive protection conferred to the progeny against clinical signs and lesions of chicken anemia.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual recognition application in accordance with Article 32 (2) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	30.07.2008
Date product first authorised in the Reference Member State (MRP only)	07.05.1990
Concerned Member States for original procedure	BE, EE, ES, FR, IE, IS, IT, LV, NL, NO, PT, SE and SI

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 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 Chicken Anaemia Virus (CAV), strain Cux-1 with $10^{4.5}$-$10^{5.5}$ $TCID_{50}$/bird dose.

The containers consist of type 1 glass bottles. The bottles have a chlorobutyl elastomer closure and are sealed with a tear off-aluminium cap**.**

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strain and formulation are justified.

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 substance is Chicken Anaemia Virus (CAV), an established substance described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is 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 European pharmacopoeia monographs where these exist, 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:

- Titration of the active substance
- Safety
- Sterility
- Quantitative test for bacterial and fungal contamination

- Mycoplasma
- Extraneous agents using embryonated hen's eggs
- Extraneous against and TRTV using chicken embryo fibroblasts Absence of EDSV
- Absence of Marek's Disease virus Absence of TRTV in Vero cells
- Residual humidity

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

The active substance is fully tested to ensure compliance with the specification immediately prior its use in 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 the reconstituted product is supported by the data provided.

III. SAFETY ASSESSMENT

Laboratory trials

Safety of one dose, an overdose and the repeated administration of one dose
The safety of the drinking water administration of one dose, an overdose and the repeated administration of one dose in the target species is demonstrated in several studies. Animals not older than the youngest age to be recommended (8 weeks) are vaccinated via the recommended route of administration (orally) with the maximum dose, a tenfold overdose and a repeated dose (7 days after the 1st vaccination) of vaccine virus at the least attenuated passage level that will be present between the master seed lot and a batch of the vaccine. The animals were daily observed and blood sampled for serology, blood cell counts and haematocrit. In addition, virus isolation in several organs was performed. Even if the youngest age claimed for vaccination is 8 weeks, the *European Pharmacopoeia* requires that the virulence of live chicken anaemia virus is also tested in young chicks (day old) in a single dose study. The day old animals were daily observed after vaccination, blood sampled for serology and haematocrit measurement at several occasions as well as examined post mortem. In addition, the body weight was measured at hatch and 14 days after vaccination.

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for laying birds or birds just before the onset of lay.

Absence of immune suppression

Chicken anaemia virus, proliferating primarily in haematopoietic precursor cells in the bone marrow and in the thymic precursor cells, is known to be immunosuppressive in young birds.

To demonstrate the absence of immunosuppression caused by AviPro THYMOVAC a study in SPF chickens of the youngest recommended age (8 weeks) was performed wherein the animals are vaccinated with a maximum dose of AviPro THYMOVAC and subsequently with a commercial dose of ND vaccine. The seroresponse towards both antigens was measured and the protection in challenge with the ND component evaluated based on clinical observation and pathological examination. No immunosuppressive influence of the vaccine AviPro THYMOVAC was detected. A further study on the impact of a vaccination with AviPro THYMOVAC on T-cell function was performed and no significant influence could be determined.

Safety of the vaccine virus in respect of spreading from vaccinated to unvaccinated chickens and in respect of reversion to virulence

The spreading potential of the vaccine and its potential for reversion to virulence has been tested with animals vaccinated at the youngest recommended age (8 weeks) with a maximum dose of WSV and put in contact to 8 week old as well as to one day old animals. Five virus passages were performed in each age group via contact infection and presence of the virus was verified after each passage

The virus could be reisolated after each passage indicating that the virus spreads via faeces. Contact with the highest passaged virus (5^{th} passage) material did not lead to (significantly) different results than the inoculation with lowest passage material (WSV) concerning the parameters haematocrit, pathological score in thymus and bone marrow as well as clinical signs. The results received with the passage material of the 1^{st} to 4^{th} passage in addition are in line with these results.

Nevertheless, the day old unprotected (SPF) animals develop pathological changes in bone marrow and/or thymus if inoculated with WSV as well as if being infected with high passage material. Even if they do not develop serious clinical signs or reductions in blood cells, a spread should be avoided. A corresponding warning is mentioned in the SPC.

Reproductive performance

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for laying birds or birds just before the onset of lay.

Dissimination in the vaccinated animal

The dissemination behaviour of CAV Cux-1 strain has been demonstrated in animals not older than the youngest age to be recommended (8 weeks) which were vaccinated via the recommended route of administration (orally) with the maximum dose of vaccine virus at the least attenuated passage level that will be present between the master seed lot and a batch of the vaccine. Virus isolation in several organs was performed. About two weeks after vaccination, all examined organs and tissues were positive for CAV with the exception of blood plasma, which was negative over the whole examination period indicating that the virus is cell bound. The virus can’t be recovered neither in oviduct nor in faeces at 4 weeks after vaccination, which would be the two possibilities to spread the virus. The warning in the SPC:

"*Vaccination should be performed from 8 weeks of age onwards, but no later than 6 weeks before the onset of lay in order to ensure that protective immunity has developed prior to the onset of lay."* is appropriate.

Interactions

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, the following warning is included in the SPC:

"No information is available on the compatibility of this vaccine with any other. Therefore the safety and efficacy of the product when used with any other (either when used on the same day or at different times) has not been demonstrated."

The investigations were performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Field studies

The safety of a maximum dose of AviPro THYMOVAC and its interaction with other vaccinations when used under field conditions has been investigated in a field trial with about 7000 animals. The safety evaluation was based on regular clinical observation, performance parameters as well as serology of vaccinates. No negative impact on the examined parameters referable to the vaccine virus could be detected.

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 negative impact on the environment can be expected from the use of the vaccine. No warnings regarding ecotoxicity are therefore required.

Warnings and precautions as listed on the product literature for its disposal are adequate to ensure safety to the environment when the product is used as directed.

Study of residues Recombination, genomic reassortment

AviPro THYMOVAC does not contain any adjuvants or preservatives. The excipients used are not pharmacologically active and are listed in Annex II of Council Regulation 2377/90.

Based on this information, no withdrawal period is proposed.

As only minor differences in isolated field strain isolates could be detected (Meenhan et al., 1992; Claessens et al., 1991; Kato et al., 1995; Phallister et. al., 1993), the recombination potential of CAV strains has to be limited. The worst case to be expected in case of recombination of vaccine virus with field virus was a new strain with the pathogenicity of the field virus.

IV CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that the vaccine is efficacious in protecting the progeny of vaccinated breeders against challenge infection and to prevent the vertical spread (egg transmission) and the horizontal spread (via faeces) of challenge virus. The protection of the progeny from vaccinated breeders has been demonstrated for one day old chicks derived from eggs by challenge, where pathology of thymus and bone marrow as well as haematokrit values were taken into account. The protection in challenge is supported by serological parameters.
The onset (4 weeks after vaccination) and duration of immunity (46 weeks after vaccination) in the breeders concerning horizontal and vertical spread of virus after challenge has been determined based on the results in challenge and , virus reisolation. The serological data are in line with the results in challenge.
In all efficacy laboratory trials, breeders were vaccinated with a minimum dose of vaccine virus from a commercial batch.

Field Trials

A field trial was performed to examine the efficacy of a minimum dose of AviPro THYMOVAC in a considerable amount of animals (about 8000) under field conditions on the basis of serology of vaccinates. The protection in challenge of breeders (vertical and horizontal transmission) and their progeny was also demonstrated in follow up trials under laboratory conditions with animals derived from this field trial.

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 Medicines Agencies (veterinary) (HMA(v)) website.

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