ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cevac Transmune Lyophilisate for Suspension for Injection with Solvent for Chicken

PuAR correct as of 28/01/2019 when RMS was transferred to HU.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0253/002/DC
Name, strength and pharmaceutical form	Cevac Transmune Lyophilisate for Suspension for Injection with Solvent for Chicken
Applicant	Ceva Animal Health Ltd Unit 3, Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB
Active substance	Live attenuated IBD virus, strain Winterfield 2512
ATC Vetcode	QI01AD09
Target species	Chickens, 18 day old embryonated broiler hatching eggs or 1 day-old broiler chickens, from hens vaccinated against IBD.
Indication for use	For the active immunisation of chickens to reduce mortality, clinical disease, weight loss and acute lesions of bursa of Fabricius associated with infection with very virulent Avian Infectious Bursal Disease (IBD) viruses. The release of the vaccine virus from the complex (and therefore immunisation) is influenced by the natural decline of maternally derived antibodies (MDA), and has been found not to occur until MDA has reached relatively low levels. The onset of clinical protection depends on the initial MDA level. In vaccinated broilers it is achieved within 1 day after the first signs of vaccine virus effect in the bursa of Fabricius. In practice, this is expected to occur between 21 and 32 days of age in target broiler flocks. Duration of immunity: up to 42 days of age. The virulent challenges tests conducted to support the claim were carried out on broilers having an MDA ELISA titre of 6,000 (1-day-old chick). Field trials carried out showed that vaccine virus replication in the bursa of Fabricius occurs in

	broilers having at hatch, MDA titre levels of up to 14,000 ELISA units, but the protection of these birds was evaluated only based on serological data and histology of the bursa of Fabricius.

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	Decentralised application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	25 July 2007
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Bulgaria, Cyprus, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Poland, Portugal, Romania, Slovakia, Spain CMSs added during Repeat Use Procedure:- Estonia, Latvia, Lithuania, Slovenia

I. SCIENTIFIC OVERVIEW

Cevac Transmune is a live vaccine containing attenuated[1] infectious bursal disease (IBD) virus. It is for the protection of chickens against clinical signs of disease, e.g. weight loss, the reduction of acute lesions of bursa Fabricius, and mortality associated with very virulent IBD virus. This is a line extension application to include one day old broiler chicks in a Marketing Authorisation that was previously indicated only for embryonated eggs. In embryonated eggs, the product is administered on the 18th day of embryonation. 0.05 ml is delivered into the amniotic sack, or rarely, into the body of the embryo, causing no decrease in hatchability. In one day old chicks, the product is delivered at 0.1 ml, subcutaneously, under the skin of the neck.

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

[1] An attenuated virus is one that has been treated so that it no longer causes disease (i.e. it is not virulent), but can still stimulate immunity replicate itself.

II. QUALITY ASPECTS

NOTE: Results from any batch testing described below originate from the first authorisation of the product, in October 2006. No additional test results were required for this Decentralised Application, which was for a line extension. No Part II (Analytical Documentation) was provided for this application.

A. Composition

The product contains live attenuated IBD virus, strain Winterfield 2512. Other substances are as follows:-

Lyophilisate
Bursal Disease Antibody (BDA)
Cyclodextrin
Sucrose
Monosodium glutamate
Potassium dihydrogen phosphate
Dipotassium hydrogen phosphate

Solvent (PBS)
Sodium chloride
Potassium chloride
Disodium phosphate dihydrate
Potassium dihydrogen phosp
hate
Water for injection

Solvent (Saline solution)
sodium chloride
water for Injection

Lyophilisate:
Cardboard box with single or 20 glass vials (Type I) of 10 ml containing 2000, 2500, 4000 or 5000 doses, and of 13.5 ml containing 8000 doses, closed with a bromobutyl stopper and sealed with aluminium caps with plastic tear-off centres.

Solvent (PBS):
Cardboard box with single, 5 or 20 plastic bottles (LDPE), of 100, 200, 250, 400 or 500 ml solvent, closed with a bromobutyl stopper and sealed with aluminium caps with plastic tear-off centres.

Solvent (Saline solution):
- Polyolefin based plastic bags equipped with infusion port, rubber stopper with flip off cap: 500 ml, 1000 ml, 5 x 500 ml, 5 x 1000 ml.
- Polyolefin based plastic bags equipped with single or double tubes, closed with injection port or rubber stopper with flip off cap: 250 ml, 500 ml, 1000 ml, 5 x 250 ml, 5 x 500 ml, 5 x 1000 ml.

Solvent (Sterile solvent):

Polyvinylchloride bag containing 200 ml, 400 ml or 800 ml in individual over-pouch.

Not all pack sizes may be marketed.

The choice of the vaccine strain is 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 live attenuated IBD virus, strain Winterfield 2512, an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin used in production comply with 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 seed 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 three consecutive runs, conforming to the specifications, were 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 checks on the appearance of the product, identity, and assay (potency) of the active substance, BDA assay, sterility, mycoplasma, extraneous agents, residual humidity and the safety of the product for chickens.

On the solvent, the tests conducted after manufacture include checks on appearance, identity and quantity of chloride ions, identity and quantity of phosphate ions, sterility and pH.

The demonstration of the batch to batch consistency is based on the results of 5 batches which were produced according to the method described in the dossier. Other supportive data were also provided to confirm further the consistency of the production process. Certificates of analysis for 3 batches of solvent were also provided.

G. Stability

Stability data on the finished product were provided for the original authorisation in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

Lyophilisate component:
The applicant provided data on three batches of the product stored refrigerated (2°C-8°C) for 27 months. At the end of this time, each batch complied with the quality control criteria. On the basis of this information, a shelf-life of 2 years was agreed.

Solvent:
The applicant provided data on three batches of the product stored at room temperature (equal or below 25°C) for 43 - 65 months. At the end of this time, each batch complied with the quality control criteria. On the basis of this information, a shelf-life of 43 months has been agreed.

The in-use shelf-life of the reconstituted vaccine is supported by the data provided. It is intended to be used within 2 hours, and the justification for this has been accepted.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Shelf life
Shelf life of the lyophilisate as packaged for sale: 2 years
Shelf life of the solvent as packaged for sale: 43 months
Shelf-life after reconstitution according to directions: 2 hours

Special precautions for storage
Lyophilisate: Store and transport refrigerated (2°C – 8°C). Protect from light.
Solvent: Store below 25°C. Do not freeze.

III. SAFETY ASSESSMENT

Laboratory trials

(Data is applicable to both original procedure and line extension procedure).

The applicant has not conducted a study to investigate the safety of the administration of one dose. Instead the safety administration of an overdose was studied to satisfy all requirements. The justification provided by the company for this was accepted. The company has also not conducted a study to investigate the safety of a repeated single dose, and the justification for this was accepted. The laboratory safety study was carried out in accordance with GLP[2] as is required. Safety was assessed clinically, over an appropriate time course, through observation and physical examination.

The adverse effects seen following administration of an overdose in healthy animals of the minimum age for which the vaccine is recommended were minor, transient and resolved within an acceptable time frame. No adverse effects were seen following subcutaneous administration of an overdose to day old SPF chicks.

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

Studies to examine immunological functions and interactions, concentrating on immunosuppression were conducted by the applicant for the original procedure. The studies were performed using SPF[3] and broiler chickens and investigated the use of *in ovo* administration and the effect of maternally derived antibodies (MDAs). The chickens were also vaccinated with an infectious bronchitis vaccine to investigate interaction with the product. The studies found that the product was immunosuppressive for SPF chicks, but not for broiler chickens.

With regard to residues, the substances in the product are all covered by the relevant guidelines or are present in such small quantities that they do not pose any concerns.

Special Requirements for Live Vaccines

Studies were provided for the original application for *in ovo* use. No additional studies were provided for the extension application, this was acceptable.

The applicant conducted two studies into the spread of Cevac Transmune vaccine strain to other chickens, for the original *in ovo* application. These studies were conducted using SPF chicks that had been vaccinated *in ovo* at the embryonation age of 18 days. The results showed that the vaccine virus is excreted through the cloaca of vaccinated chickens and spreads to unvaccinated birds.

The applicant also conducted a study to investigate the dissemination of the Cevac Transmune vaccine strain. This study was performed using SPF chicks

[2] Good Laboratory Practice.
[3] Specific Pathogen Free.

vaccinated *in ovo* at the embryonation age of 18 days. The study found that the vaccine virus was undetectable in the oral swab samples during a 21 day period, and was present in cloacal swabs on 7 days post inoculation. Virus was detectable in bursa on day 7 onwards until day 21, whereas in spleen and thymus it was detectable on days 7 and 11 post vaccination.

The applicant has conducted two studies investigating the possibility of the product vaccine strain to revert to virulence, and the general safety and damage to the bursa of Fabricius of IBD virus in SPF chicks. The first study showed that the virus obtained at the end of the study was the same strain as at the beginning (Winterfield 2512), indicating that the vaccine virus does not revert to virulence. The second study showed that when comparing the clinical signs there was no difference between birds inoculated with the product and birds inoculated with a homogenate infected with the vaccine IBD virus. The applicant concluded that the vaccine virus is stable and does not revert to virulence.

Field studies

The applicant conducted two field trials for safety and efficacy with regard to the original application.

The aim of the first study was to test the safety of the vaccine and compare it to an already authorised Infectious Bursal Disease (IBD) virus product, which was administered to the chickens orally. The first study was performed using commercial broiler chickens split into two groups. In Phase I the first group was inoculated *in ovo* at the embryonation age of 18 days, and the second group were inoculated with a placebo. In Phase II the birds were allocated to three separate animal houses, and birds in house one were given the reference vaccine on day 22.

Safety was assessed on bursa to body weight ratios, the European broiler index, pathology, serology and histology.

The results showed that the product when used with the reference vaccine had no impact on the hatching ratio, no difference in the European broiler index, no adverse effects, and the virus release was confirmed on day 22. The applicant concluded that the product when administered *in ovo* is safe in broiler chickens in field conditions.

The aim of the second study was to test the safety of the vaccine and compare it to an already authorised IBD virus product, which was administered to the chickens orally. In Phase I the first group was inoculated *in ovo* at the embryonation age of 18 days, and the second group was inoculated with a placebo. In Phase II the birds were allocated to eight separate animal houses, and birds in houses 6 and 9 were given the IBD vaccine on day 19. Birds in houses 10 and 11 were given the reference vaccine on day 23.

Safety was assessed on bursa to body weight ratios, the European broiler index, pathology, serology and histology.

The results showed that the product when used with the reference vaccine had no impact on the hatching ratio, no difference in the European broiler index, no adverse effects, and the virus release was confirmed on day 26. The applicant

concluded that Cevac Transmune when administered *in ovo* is safe in broiler chickens in field conditions.

An additional study was performed in order to validate the extension application for use of the product in one day old chicks. The assay was also relevant for efficacy studies, and is described in Part IV. A suitable number of day old, commercial broiler chicks were placed into five matched, treatment group pairs. Birds received either the product or a competitor vaccine. Blood sampling and analysis for viral antigens, (both vaccinate and wild type) were performed. No unduly adverse reactions due to the vaccinations were observed, and production parameters were similar between the product and competitor product.

Ecotoxicity

An environmental risk assessment for the original product indicated that the risk to the environment from the use of the product in chickens is minimal. Additional information was provided for the extended product, outlining additional parameters relevant to the product when used in day old chicks. The applicant stated that shedding of the virus may occur later in day old chicks than in embryonated eggs, that the virus is not likely to disseminate or survive where appropriate disinfection and cleaning practises are used, there is no evidence of change in host range because of attenuation, and that there are no toxic effects from the product components. Any spillage would cause only minor consequences with regard to toxicity. Self-injection by the operator would cause negligible hazard, as the product has no known harmful effect on humans.

General advice for the disposal of any unused product is provided in the SPC.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

The applicant conducted three laboratory studies for the original application.

The first study was to investigate compatibility between the product and an infectious bronchitis (IB) vaccine in SPF chickens. Chickens were split into two groups, and in each group there were vaccinated chickens and unvaccinated controls. The vaccinated chickens were inoculated with the product *in ovo* at 18 days of embryonation and an infectious bronchitis vaccine at 1 day old via the intraocular route.

The study showed that IBD vaccination as recommended, does not affect the efficacy of infectious bronchitis vaccination at 1 day old. However infectious bronchitis vaccination at one day of age, following vaccination as recommended, did delay the onset of protection against IBD. The compatibility of the two vaccines was not reciprocal.

The second study was to investigate the efficacy of the product in the presence of maternally derived antibodies. The eggs were split into two groups. The first group were vaccinated *in ovo* with Cevac Transmune of varying potencies at 18

days of embryonation. The second group were left as unvaccinated controls. All birds were challenged at 21, 28 and 42 days of age.

The study showed that seroconversion[4] was starting from 17 days of age, with demonstrated onset at 21 days that lasted until day 42. The best weight gain was with the proposed potency.

The third study was to investigate the efficacy of model vaccines of the product at different compositions on broiler chicks with IBD virus maternal antibodies. The eggs were split into two groups. The first group was vaccinated with various model vaccines of Cevac Transmune *in ovo* at 18 days of embryonation. The second group was left as unvaccinated controls. All birds were challenged at 28, 35 and 43 days of age.

The study showed that seroconversion[5] was achieved by 24 days of age with the proposed model of the product and one sub-potent batch. Seroconversion was delayed in the proposed formulation for Cevac Transmune that had a lower limit of bursal disease antibody. The onset of immunity was by 24 days of age, and batches of the vaccine that are formulated below the specifications were shown to be efficacious.

An additional study was also performed in order to extend the authorisation of the product for use in day old broiler chicks. The efficacy of subcutaneously administered Cevac Transmune in broiler and SPF chicks was investigated. A suitable number of groups of day old chicks were vaccinated with Cevac Transmune prior to two challenges with virulent IBDV. A control group remained unvaccinated.

Both SPF and broiler negative controls succumbed to challenge, but vaccinated birds were 100% protected.

Field Trials

Two field trials were conducted by the applicant for the original application, for safety and efficacy. The reference vaccine mentioned is the same as the one used and described in the safety section of this report.

The first trial was performed using commercial broiler chickens split into two groups. In Phase I the first group was inoculated *in ovo* at the embryonation age of 18 days, and the second group were inoculated with a placebo. In Phase II the birds were allocated to three separate animal houses, and birds in house one were given the reference vaccine on day 22.

In the second study commercial broiler chickens were used and split into two groups. In Phase I the first group was inoculated *in ovo* at the embryonation age of 18 days, and the second group were inoculated with a placebo. In Phase II the birds were allocated to eight separate animal houses, and birds in houses 6 and 9 were given the reference vaccine on day 19. Birds in houses 10 and 11 were given the reference vaccine on day 23. Both trials showed that seroconversion[5] does occur in the field.

[4]The development of detectable specific antibodies to micro-organisms in the serum as a result of infection or immunisation.

Efficacy has been demonstrated with an onset of immunity at 21 days of age and a duration of immunity of at least 42 days. It has been shown that the administration of a batch not made to specification induced protection against IBD.

In order that the product could be authorised for use in day old chicks, a further field study was conducted. The study, which was relevant for the safety of the product and is referred to in part III, Safety, was conducted in a suitable number of day old commercial broiler chicks, contained in five matched groups. Birds received either the product or a competitor vaccine. A significant serological response was seen in groups treated with either the product or the competitor product, with no significant difference seen between the two.

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)