Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cevac MD HVT suspension and solvent for suspension for injection for chickens

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0264/001/DC
Name, strength and pharmaceutical form	Cevac MD HVT suspension and solvent for suspension for injection for chickens
Applicant	Ceva-Phylaxia Co. Ltd. Budapest Szállás u. 5. 1107 HUNGARY
Active substance(s)	Cell-associated live turkey herpes virus (HVT, Marek's disease virus), serotype 3, strain FC-126
ATC Vet code	ATCvet code: QI01AD03
Target species	Chickens and embryonated chicken eggs
Indication for use	For active immunisation of 18-day-old embryonated chicken eggs or one-day-old chicks to reduce mortality, clinical signs and lesions caused by mild and virulent strains of Marek's disease virus. Onset of immunity: 9 days after the vaccination. Duration of immunity: A single vaccination is sufficient to provide protection during the risk period of infection with Marek's disease.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	19/10/2016
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	BE, BG, CY, CZ, DE, DK, EE, EL, FR, HR, HU, IE, IT, LT, LV, NL, PL, PT, RO, SI, SK, UK

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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 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 2000-8000 PFU (Plaque forming units) of cell-associated live turkey herpes virus (HVT, Marek's disease virus) serotype 3, strain FC-126. Following, the virus suspension and solvent excipients are listed:
Frozen virus suspension:

EMEM
L-glutamine
Sodium bicarbonate
Hepes
Bovine serum
Dimethyl sulfoxide
Water for injection

Solvent:

- Sucrose
- Casein hydrolisate
- Sorbitol
- Dipotassium hydrogen phosphate
- Potassium dihydrogen phosphate
- Phenol red
- Water for injection

The container/closure system for the frozen suspension (containing the antigen) are 2 ml, flame sealed, glass ampoules. The containers for the solvent are polyvinylchloride bags. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strain and formulation are properly explained. Neither adjuvant nor preservative are included in the vaccine and it 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.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is cell-associated live turkey herpes virus, serotype 3, strain FC-126 (HVT, Marek's disease virus), an established substance described in the European Pharmacopoeia. The active substance is 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 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. and EMA Guidelines; 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 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 potency, freedom from extraneous agents and sterility.

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. Results of 9 batches of diluents are also provided. 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 during 2 years.
Stability data on the solvent have also been provided when stored in polyvinylchloride bags demonstrating the stability of the solvent during 3 years.

The in-use stability of 2 hours of the reconstituted vaccine according to directions is supported by the data provided.

H. Genetically Modified Organisms

Non applicable

J. Other Information

The manufacturing of this cell-associated vaccine is well described and conditions of transport and handling are also clearly indicated.

III. SAFETY ASSESSMENT

Vaccine batches used in safety studies:

Batch	Study
EU MSV+1	- Overdose safety by subcutaneous route in day old SPF chickens - Overdose safety and residual pathogenicity by in-ovo route - Shed and spread between chickens and between chicken and turkeys - Shed and spread between chickens and between chickens and turkeys
Batch 1	- Overdose safety and spread in turkeys - Overdose safety and spread in ducks - Overdose safety and spread in quails - Overdose safety and spread in guinea-fowls - Overdose safety and spread in pheasants - Overdose safety and spread in pigeons
Batch 2	- Safety and efficacy field trials

Laboratory trials

The safety of the administration of one dose and an overdose in the target animal is demonstrated in laboratory studies using both administration routes: subcutaneous and in ovo. Also the age of the animals was set according to the vaccination schedule. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. As no problems were found, the absence of symptoms after the administration of a 10-fold dose is stated in the SPC.

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.

For the live strain included in the vaccine:
Specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, of the vaccine strain as they are required by Directive 2001/82 as amended. According to the results of these studies, the following is included in the SPC:

"*The vaccine strain was shown to be excreted by chickens for 46 days. The excreted vaccine strain was not harmful in turkeys in safety trials; however, special precautions should be taken to avoid spreading of the vaccine strain to turkeys. A ten-fold overdose was safe for turkeys, ducks, quails, guinea fowls, pheasants and pigeons.*

No spread was demonstrated between chickens."

There is not adjuvant included in the vaccine. The excipients used are according to Commission Regulation (EU) No 37/2010. Based on this information, 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

Two combined field safety and efficacy study was conducted at two commercial farm sites in Hungary. After in-ovo and subcutaneous use, the vaccine was found to be safe based on the main and secondary safety parameters: EPEF, hatching ratio, hatchability and local reactions.

Summary of safety trials/studies included in the application:

Test	Nº an.*	Dose	Batch	Route	GLP
Overdose 1	40	10x	EU-MSV+1	SC	Yes
Overdose 2	50	10x	EU-MSV+1	*In ovo*	Yes
Spread/shed	25	10x	EU-MSV+1	*In ovo*	Yes
Spread (turkeys)	20	10x	Batch 1	SC	Yes
Spread (ducks)	20	10x	Batch 1	SC	Yes
Spread (quails)	21	10x	Batch 1	SC	Yes
Spread (Guinea fowls)	20	10x	Batch 1	SC	Yes
Spread (Pheasants)	20	10x	Batch 1	SC	Yes
Spread (Pigeons)	20	10x	Batch 1	SC	Yes
Field trial 1	> 29.900*	1x	Batch 2	SC/ *In ovo*	GCP
Field trial 2	> 22.000*	1x	Batch 2	SC/ *In ovo*	GCP

* On Day 0, some of the chicks were involved in complementary laboratory efficacy trials.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.B Clinical Studies

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that the vaccine can be used for active immunisation of 18-day-old embryonated chicken eggs or one-day-old chicks to reduce mortality, clinical signs and lesions caused by mild and virulent strains of Marek's disease virus. 9 days after vaccination, the onset of immunity is established and vaccinated birds are protected during the risk period of infection with Marek's disease.

Vaccine Batch 2 and Batch 3 were chosen to demonstrate the efficacy during the laboratory trials. Minimum potency of the vaccine for the efficacy trials was used at is required by Ph. Eur. and EMA Guidelines. The challenge strain used in these laboratory studies can be considered as virulent and a control non-vaccinated group was included. The recommended dose for *in ovo* application is 0.05 ml for 18 days old embryonated eggs and 0.2 ml for subcutaneous application under the skin of the neck for day old chickens. All studies were conducted to comply with the recommended volume and more than 30 embryonated chicken eggs or chickens per group were used. The minimum recommended dose for vaccination is 2,000 PFU. Clinical signs and mortality during post-challenge period were observed and samples were taken for histological examination.

Validity criteria were achieved and the relative protection percentage showed that the vaccine is efficacious against Marek's disease virus challenge in embryonated chicken eggs and SPF chickens under laboratory circumstances

Field Trials

Two combined field safety and efficacy study was conducted at two commercial farm sites in Hungary. After in-ovo and subcutaneous use, the vaccine was found to be safe based on the main and secondary safety parameters: EPEF, hatching ratio, hatchability and local reactions.

The CEVAC MD HVT vaccine was efficacious based on the following observations:
- No clinical signs of Marek's disease were observed during the field trials.
- No Marek's disease was diagnosed on the field during the weekly necropsies
- No Marek's disease was diagnosed by histological examination.
- The mean body weight and feed conversion ratio were not affected either the disease or the vaccine.

Summary of efficacy trials/studies included in the application:

Test	Nº an.	Dose	Batch	Route	Quality assurance
Onset of immunity 1 (SPF chickens)	65	1x	Batch 2	SC	Yes
Onset of immunity 2 (SPF embryos)	64	1x	Batch 3	*In ovo*	Yes
Onset of immunity 3 (Broilers chickens)	99	1x	Batch 2	SC	Yes

Test	Nº an.	Dose	Batch	Route	Quality assurance
Onset of immunity 4 (Commercial eggs)	100	1x	Batch 2	*In ovo*	Yes
Field trial 1	> 29.900	1x	Batch 2	SC/ *In ovo*	Yes (GCP)
Field trial 2	> 22.000	1x	Batch 2	SC/ *In ovo*	Yes (GCP)
Efficacy in broilers (from Field trial 2)	99	1x	Batch 2	SC	Yes
Efficacy in broilers (from Field trial 2)	96	1x	Batch 2	*In ovo*	Yes
Efficacy in broilers (from Field trial 1)	99	1x	Batch 2	SC	Yes
Efficacy in broilers (from Field trial 1)	99	1x	Batch 2	*In ovo*	Yes

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 (www.hma.eu).

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>

or

Complete this section for extensions to the same VPA range or defined, significant variations, using the table shown below.

Some examples of significant changes in safety or efficacy data are:

- *Changes to pharmacokinetic data leading to a change in the SPC*
- *Changes to toxicological data leading to a change in the SPC*
- *Changes to user safety warnings*
- *Changes to ecotoxicological information as given in the SPC or changes to disposal warnings*
- *New residue studies in new target species or tissues*
- *Reassessment of residue data or new studies resulting from changes to MRL*
- *Changes to withdrawal period*
- *Changes to target species*
- *Changes to target species tolerance data leading to change in warnings/precautions for target species*
- *New or changed indications*

Significant changes in administrative or quality data include any Type II change, which affects the initial report. The following Type IA or IB changes may also apply:

- *Name of product [Type IA: 2]*
- *Name of active substance [Type IA: 3}*
- *MAH [Type IA: 1]*
- *Composition of the medicinal product [Type IB: 18, Type IA/B: 25, 34, 35, 39]*
- *Container/closure system [Type 1/B: 26, 28, 29, 36, 41, 43]*
- *Method of preparation [Type 1B: 33]*
- *Active substance specification [Type IB: 25]*
- *CEP [Type IA/B: 15]*
- *Re-test period or storage conditions of active substance [Type IB: 17]*
- *Excipient specifications [Type 1A/B: 25]*
- *Packaging materials[Type 1A/B: 28, 29, 36, 41, 43]*
- *TSE [Type 1A: 16, 22]*
- *Shelf-life or storage conditions of the finished product [Type 1B: 42]*

Quality changes

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
<Example: Change to active substance specification> (MS/V/XXX/X/IB/XX)	N/A	

Safety/efficacy changes

Summary of change **(Type; application number)**	**Section updated in Module 3**	**Approval date**
<Example: Addition of target species - pigs> (MS/V/XXX/X/II/XX)	<IIIA> <IIIB> <IV>	