MINISTERIO DE SANIDAD
agencia española de medicamentos y productos sanitarios

DEPARTAMENTO DE MEDICAMENTOS VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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

DECENTRALISED PROCEDURE

DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cevac MD Rispens concentrate and solvent for suspension for injection for chickens

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0312/001/DC
Name, strength and pharmaceutical form	Cevac MD Rispens concentrate and solvent for suspension for injection for chickens
Applicant	Ceva Salud Animal Avenida Diagonal, 609-615, 9ª planta 08028 Barcelona SPAIN
Active substance(s)	Cell-associated live Marek's disease virus (MDV) serotype 1, strain CVI-988
ATC Vetcode	QI01AD03
Target species	Chickens
Indication for use	For active immunisation of one-day-old future layer chicks to reduce mortality, clinical signs and lesions caused by very virulent strains of Marek's disease virus.

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MODULE 2

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

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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 (so called full application)
Date of completion of the original decentralisedprocedure	06/05/2020
Date product first authorised in the ReferenceMemberState (MRP only)	-
Concerned Member States for original procedure	AT, BE, BG, HR, CY, CZ, DK, EE, FI, FR, DE, EL, HU, IE, IT, LV, LT, NL, PL, PT, RO, SK, SI, SE, 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. Since the vaccine is marketed frozen in liquid nitrogen containers, the special precautions to be taken by the person administering the veterinary medicinal product to animals are specifically detailed. 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. Qualitative and quantitative particulars

The product contains Cell-associated live Marek's disease virus (MDV) serotype 1, strain CVI-988 as active substance. The excipients are well known materials and specifically intended to protect frozen cells. The vaccine is marketed with a specific solvent and its excipients are also described.

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The container for the concentrate consists of Type I glass ampoule containing 1000, 2000 or 4000 doses. Solvent containers are polyvinylchloride bag containing 200 ml, 400 ml or 800 ml in individual over-pouch. Specific conditions for the maintenance of the frozen suspension during storage and transport are specified in the SPC.

The choice of the vaccine strain, formulation and the absence of preservative 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 and the product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is Marek's disease virus, serotype 1, strain CVI-988, an established substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice. The vaccine contains 800-5000 PFU (Plaque Forming Units) per dose of 0,2 ml. Following, the concentrate (virus suspension) and solvent excipients are listed:

Concentrate: EMEM, L-glutamine, Sodium bicarbonate, Hepes, Bovine serum, Dimethyl sulfoxide and Water for injection.

Solvent: Sucrose, Casein hydrolysate, Sorbitol,Dipotassium hydrogen phosphate, Potassium dihydrogen phosphate, Phenol red and Water for injection.

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.

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.

Starting materials of non-biological origin used in production comply with Eur. Ph. 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 Guidelines.

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The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

D. Control tests during production

The tests performed during production are described and the results of various consecutive runs, conforming to the specifications, are provided. In order to ensure that quality of the product is consistent from batch to batch and to demonstrate conformity with specifications, protocols of various consecutive batches (for both the suspension and the solvent) including the results for all tests performed during production and on the finished product have been provided.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular appearance, pH, titration, identification, sterility, absence of mycoplasmas and absence of extraneous agents. For the solvent, appearance pH, sterility, osmolarity and filling volume are also controlled.

The demonstration of the batch to batch consistency is based on the results of 4 batches produced according to the method described in the dossier. Also, 9 batch protocols of different presentations of the solvent are provided. Other supportive data provided, as the results for all tests performed during production, confirm the consistency of the production process.

F. 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.

The 2-hours in-use shelf-life of the reconstituted vaccine is supported by the data provided.

G. Other Information

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III. SAFETY ASSESSMENT

Vaccine batches used in safety studies:

Batch	Manufacturing data	Study
MSV	2014	- Residual pathogenicity of the vaccine on SPF chickens - Shed, spread and dissemination of the vaccine on SPF chickens - Increase in virulence test of vaccine on SPF chickens - Increase in virulence test of vaccine in commercial layers - Safety interaction test of Vectormune ND and the vaccine on SPF chickens
0210CF	October 2014	- Safety test of the vaccine (5000 PFU) on commercial layer chickens - Spread test of the vaccine from vaccinated to non-treated commercial layer chickens
0204DF	March 2015	- Safety and efficacy field trial
0104DF	March 2015	- Safety and efficacy field trial - Clinical field trial of mixed administration of the vaccine and Vectormune ND

Laboratory trials

The safety of the administration of an overdose in the target animal is demonstrated in laboratory studies on SPF chickens using the subcutaneous administration route. 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 section 4.10 of 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, recombination or genetic reassortment 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:

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"*Spread of the vaccine strain was demonstrated between chickens and may occur from 14 days after vaccination. Vaccinated chickens may excrete the vaccine strain for at least 112 days following vaccination. During this time, the contact of immunosuppressed and unvaccinated chickens with vaccinated chickens should be avoided.*

The excreted vaccine strain is safe in non-vaccinated 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.

The interaction of the vaccine with VECTORMUNE ND was studied. According to the results of these studies, the following is included in the SPC:

"Safety and efficacy data are available which demonstrate that this vaccine can be mixed and administered with Vectormune ND by subcutaneous application.

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product except the product mentioned above. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis."

Field studies

Two combined field safety and efficacy study was conducted at two commercial farm sites in Hungary. After subcutaneous use, the vaccine was found to be safe based on the main and secondary safety parameters: mortality, necropsy and histology results, individual body weight, feed consumption and local reactions.
Furthermore, to support the claim on associated use of CEVAC MD RISPENS administered with Vectormune ND the safety interaction was also assessed in the frame of a combined safety-efficacy field trial performed in a commercial layer farm in Hungary.

Summary of safety trials/studies included in the application:

Test	Reference	Nº an.*	Dose	Batch	Route	GLP
Overdose (SPF)	CLI-219-2014	120	10x	MSV	SC	Yes
Overdose (layers)	CLI-005-2016	42	10x	0210CF	SC	Yes
Spread/shed/dissemination (SPF)	CLI-216-2014	124	10x	MSV	SC	Yes
Spread (layers)	CLI-006-2016	120	1x	0210CF	SC	Yes
Reversion to virulence(SPF)	CLI-021-2015	139	1x	MSV	In ovo	Yes
Reversion to virulence (layers)	CLI-171-2016	135	1x	MSV	SC	Yes
Reversion to virulence(SPF)	CLI-254-2018	140	1x	MSV	SC	Yes
Interaction with Vectormune ND (SPF)	CLI-158-2015	126	1x	MSV	SC	Yes
Field trial	CLI-092-2017	22,460	1x	0204DF	SC	GCP
Field trial	CLI-103-2017	27.000	1x	0104DF	SC	GCP
Field trial	CLI-105-2017	20,030	1x	0104DF	SC	GCP

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

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Environmental Assessment

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 control procedures are needed in addition to the national requirements of handling and disposal of residual medicines.

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

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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 can be used for active immunisation of one-day-old chicks to reduce mortality, clinical signs and lesions caused by very 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 batches 0210CF, 0204DF and 0104DF were chosen to demonstrate the efficacy during the laboratory and the field trials. Minimum protective dose of the vaccine for the efficacy trials was used at is required by Ph. Eur. and EMA Guidelines (800 PFU). All the studies were performed with batches at a passage level of MSV+5, using the highest allowed passage level. The challenge strain used in these laboratory studies can be considered as a very virulent and a control non-vaccinated group was included. The recommended dose is 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 chickens per group were used. The minimum recommended dose for vaccination is 800 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 commercial layers and SPF chickens under laboratory circumstances.

Summary of efficacy trials/studies included in the application:

Animals Groups Number Age	**Antibody status**	**Vaccine: route of admon**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results: Cases/total (%)**			**% Rate of protection**
Study CLI-123-2015					Treated	Control Layers	Control SPF	
Chicken 1 day old Vaccinates:40 Controls:31	SPF	Strain CVI -988 SC	9 days pv Strain RB1B	70 days - Mortality - Pathology - Histology	0/40 (0) 1/40(2.5) 0/40 (0)	15/31 (48.4) 21/31 (67,7) 8/8 (100)	N/A	Treated:100 Control:16.1
Animals Groups Number Age	**Antibody status**	**Vaccine: route of admon**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results: Cases/total (%)**			**% Rate of protection**
Study CLI-124-2015					Treated	Control layers	Control SPF	
Chicks-day-old Vacc layers:41 Contr layers:31 Control SPF:31	Commercial Layers and SPF	Strain CVI -988 SC	9 days pv Strain RB1B	70 days - Mortality - Pathology - Histology	1/41 (2.4) 1/41(2.4) 0/41 (0)	21/31 (67.7) 26/31 (83.9) 1/31 (3.2)	15/31 21/31(67.7) 5/31	Treated:97.6 Layer(C)12.9 SPF(C) 16.1
Animals	**Antibody**	**Vaccine:**	**Challenge:**	**Follow up:**	**Results:**			**% Rate of**

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Groups Number Age	**status**	**route of admon**	**Day post-vaccination**	**Duration Endpoints***	**Cases/total (%)**			**Protection**
Study CLI-174-2015					Treated	Control layers	Control SPF	
Chicks-day-old Vacc layers:40 Contr layers:40 Control SPF:39	Commercial Layers and SPF	Strain CVI -988 +rHVT/ND SC	9 days pv Strain RB1B	70 days - Mortality - Pathology - Histology	2/40 (5) 1/40(2.5) 1/40(2.5))	25/40 (62.5) 39/40 (97.5) 0/40 (0)	26/39(66.7) 35/39 (89.7) 3/39(7.7)	Treated:95 Layer(C)2.5 SPF(C) 2.6
Animals Groups Number Age	**Antibody status**	**Vaccine: route of admon**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints***	**Results: Cases/total (%)**			**% Rate of Protection**
Study CLI-195-2015					Treated	Control layers	Control SPF	
Chicks-day-old Vacc layers:35 Contr layers:35 Control SPF:35	Commercial Layers and SPF	Strain CVI -988 +rHVT/ND SC	9 days pv Strain MD70 i.p. route	70 days - Mortality - Pathology - Histology	2/35(5.7) 0/35(0) 0/35(0)	13/35(37,1) 31/35(88.5) 2/35(5,7)	33/35(94.3) 28/35 (80) 3/35(8.5)	Treated:100 Layer(C)5.7 SPF(C) 5.7
Animals Groups Number Age	**Antibody status**	**Vaccine: route of admon**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints**	**Results: Cases/total (%)**			**% Rate of Protection**
Study CLI-127-2015					Treated	Control layers	Control SPF	
Chicks-day-old Vacc layers:100 Contr layers:35 Control SPF:12	Commercial Layers and SPF	Strain CVI -988 +rHVT/ND SC	18 weeks pv Strain NDV Herts 33/56 IM route	14 days - Mortality	0/24 (0)	12/12 (100)	12/12 (100)	Treated:100 Layer(C)0 SPF(C) 0
Animals Groups Number Age	**Antibody status**	**Vaccine: route of admon**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints**	**Results: Cases/total (%)**			**% Rate of Protection**
Study CLI-129-2015					Treated	Control layers	Control SPF	
Chicks-day-old Vacc layers:100 Contr layers:35 Control SPF:20	Commercial Layers and SPF	Strain CVI -988 +rHVT/ND SC	3 weeks pv Strain NDV Herts 33/56 IM route	14 days - Mortality	0/24 (0)	4/12 (100)	12/12 (100)	Treated:100 Layer(C)66.6 SPF(C) 0

Field Trials

Two combined field safety and efficacy study was conducted at two commercial farm sites in Hungary. As there wasn´t any outbreak during the trial, the efficacy was assessed in a laboratory challenge, and an extra group with SPF birds was included. In addition, two test was performed as a complementary efficacy test of the field trials: study CLI-093-2017 and study CLI-104-2017.

After subcutaneous use, the vaccine was found to be efficacious based on the main and secondary efficacy parameters: mortality, pathological and histological findings.

Summary of efficacy trials/studies included in the application:

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Animals Groups Number Age	**Antibody status**	**Vaccine: route of admon**	**Challenge if appropriate: Day post-vaccination Strain**	**Follow up: Duration Endpoints**	**Results: Cases/total (%)**			**%Rate of protection**
Study CLI-092-2017					Treated	Control + layers	Control – SPF	
Chicks-day-old Vacc; 10220 Positive Control:12240 Negative Control: 35	Commercial Layers and SPF	CVI-988 Positive Control: RISMAVAC +CA126 SC	115 days pv Strain RB1B	14 days - Mortality	8/35 (22.85)	34/35 (97.1)	34/35 (97.1)	Treated:77.1 Control+:2.9 Control-: 2.9
Animals Groups Number Age	**Antibody status**	**Vaccine: route of admon**	**Challenge if appropriate: Day post-vaccination Strain**	**Follow up: Duration Endpoints**	**Results: Cases/total (%)**			**%Rate of Protection**
Study CLI-093-2017					Treated	Control layers	Control SPF	
Chicks-day-old Vacc layers; 35 Control layer:40 SPFControl: 45	Commercial Layers and SPF	CVI-988 Positive Control: RISMAVAC +CA126 SC	9 days pv Strain RB1B IP route	71 days - Mortality -Pathology	6/35(17.1 8/35 (22.9	28/35(80) 34/35 (97.1	24/35(68,6) 43/35(97)	Treated:77.1 Control+:2.9 Control-: 2.9
Animals Groups Number Age	**Antibody status**	**Vaccine: route of admon**	**Challenge if appropriate: Day post-vaccination**	**Follow up: Duration Endpoints**	**Results: Cases/total (%)**			**%Rate of Protection**
Study CLI-103-2017					Treated	Control + layers	Control - SPF	
Chicks-day-old Vacc; 13030 Positive Control:14000 Negative Control: 35	Commercial Layers and SPF	CVI-988 Positive Control: CRYOMAREX RISPENS SC	115 days pv Strain RB1B	14 days - MD + (based on pathology an	3/35 (8.6)	34/35 (97.1)	35/35 (100)	Treated:91.4 Control+:2.9 Control-: 0
Animals Groups Number Age	**Antibody status**	**Vaccine: route of admon**	**Challenge if appropriate: Day post-vaccination**	**Follow up: Duration Endpoints**	**Results: Cases/total (%)**			**%Rate of Protection**
Study CLI-104-2017					Treated	Control + layers	Control - SPF	
Chicks-day-old Vacc layers; 35 Control layer:40 SPFControl: 40	Commercial Layers and SPF	CVI-988 SC	9 days pv Strain RB1B IP route	71 days - MD + (based on pathology an	3/35 (8.6)	34/35 (97.1)	35/35 (100)	Treated:91.4 Control+:2.9 Control-: 0

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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.

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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).

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