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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

FILAVAC VHD K C+V suspension for injection for rabbits

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0315/001/MR
Name, strength and pharmaceutical form	FILAVAC VHD K C+V suspension for injection for rabbits
Applicant	FILAVIE 20, LA CORBIERE 49450 ROUSSAY FRANCE
Active substances	0.5 ml dose of vaccine contains: Rabbit Haemorrhagic Disease Virus strain LP.SV.2012 (variant strain 2010, RHDV2), inactivated....min 1 PD90% * Rabbit Haemorrhagic Disease Virus strain IM507.SC.2011 (classical strain, RHDV1), inactivated....min 1 PD90% * Adjuvant: Aluminium hydroxide (Al ³⁺)0.35 mg (*)Protective dose at least 90% of the vaccinated animals.
ATC Vetcode	QI08AA01
Target species	Rabbits
Indication for use	For active immunisation of rabbits from 10 weeks of age, to reduce mortality due to rabbit haemorrhagic disease caused by classical (RHDV1) and type 2 (RHDV2) virus strains.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on
the website <http://www.ircp.anmv.anses.fr/>

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original procedure	29th September 2015
Date product first authorised in the Reference Member State (MRP only)	29th September 2015
Concerned Member States for original procedure	Belgium, Denmark, Finland, Germany, Italy, Luxemburg, Netherlands, Norway, Portugal, Sweden, Spain, United Kingdom

I. SCIENTIFIC OVERVIEW

The vaccine FILAVAC VHD K C+V is considered as a MUMS product and therefore the Guideline on Data requirements for Immunological veterinary medicinal products intended for minor use or minor species/limited markets (EMA/CVMP/IWP/123243/2006-Rev.2) was taken into consideration for the assessment of the quality, safety and efficacy parts of the dossier.

The vaccine is a multivalent inactivated viral vaccine which is indicated for the immunisation of rabbits from 10 weeks of age, to reduce mortality due to rabbit haemorrhagic disease caused by classical (RHDV1) and type 2 (RHDV2) virus strains.

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 reactions observed are indicated in the SPC (Summary of Product Characteristics).

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

II. QUALITY ASPECTS

A. *Composition*

0.5 ml dose of vaccine contains:

Rabbit Haemorrhagic Disease Virus strain LP.SV.2012 (variant strain 2010, RHDV2), inactivated.....min 1 PD90% *

Rabbit Haemorrhagic Disease Virus strain IM507.SC.2011 (classical strain, RHDV1), inactivated.....min 1 PD90% *

Adjuvant:

Aluminium hydroxide (Al³⁺)0.35 mg

(*)Protective dose at least 90% of the vaccinated animals.

The vaccine is filled in glass type I containers, closed with a nitrile rubber stopper and sealed with an aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains is justified.

The inactivation process and the control of inactivation are correctly validated.

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 practices in 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*

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 "Table of extraneous agents to be tested for in relation to the general and species-specific guidelines on production and

control of mammalian veterinary vaccines" (Note for Guidance III/3427/93, 7Blm10a).

Seed lots have been produced 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 4 consecutive runs (1 dose, 50 doses and 2 vials of 200 doses), conforming to the specifications, are provided.

F. *Control Tests on the Finished Product*

The tests performed on the final product are in line with the relevant requirements; any deviation from these requirements is justified. The tests performed are as follows:

Suspension

- appearance
- pH
- aluminium assay
- free formaldehyde assay
- sodium disulfite assay
- volume
- identification
- RT-PCR quantification
- potency test
- sterility: according to Ph. Eur. 2.6.1

The demonstration of the batch to batch consistency is based on the results of 4 batches of vaccine (1 dose, 50 doses and 2 vials of 200 doses) produced according to the method described in the dossier.

G. *Stability*

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 (24 months) when stored under the approved conditions (at 2-8° C).

The vaccine must be used maximum 2 hours after dilution.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the subcutaneous administration of one dose of vaccine in the target species is demonstrated in a laboratory study. Safety was assessed in Specific Pathogen Free (SPF) rabbits 4 weeks old (20 vaccinees) and 10 weeks old (20 vaccinees), during 6 months, through observation and physical examination. A control group of non-vaccinated animals (4 weeks old: 20 animals and 10 weeks old: 20 animals) was included in the study.

The safety of the subcutaneous administration of an overdose and the repeated administration of one dose in the target species is demonstrated in two laboratory studies. Safety was assessed clinically in eight Specific Pathogen Free (SPF) rabbits 4 weeks old and in twelve dwarf rabbits 11 weeks old, during 30 days, through observation and physical examination.

In both studies, the investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Overall, the vaccine proved to be well tolerated in the target species. The local and systemic reactions observed are described in the SPC (Summary of Product Characteristics) and package leaflet under "adverse reactions".

Effects on reproductive performance were examined in a field trial. As the vaccine proved to be safe in pregnant rabbits, the vaccine can be used during pregnancy. A corresponding note is included in the SPC and package leaflet.

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

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

Details are given in the Summary of Product Characteristics (SPC) as follows:

4.6 Adverse reactions (frequency and seriousness)

Very common: a temporary increase in body temperature of up to 1.6°C can be observed one day after vaccination.

Very common: immunization may be followed by a limited local reaction (subcutaneous nodule, the size of which was up to 10 mm in diameter in the double dose study) which may be palpable for at least 52 days and which disappears without treatment.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s);*
- common (more than 1 but less than 10 animals in 100 animals treated);*
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated);*
- rare (more than 1 but less than 10 animals in 10,000 animals treated);*
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).*

4.7 Use during pregnancy, lactation or lay

Pregnancy:

During a field trial, no case of abortion was noted after administration of the vaccine to pregnant animals.

Use only according to the benefit-risk assessment by the responsible veterinarian.

Fertility:

The influence of the vaccination on the fertility of rabbits has not been investigated.

4.8 Interaction with other medicinal products and other forms of interaction

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. 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.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

No adverse reactions other than those referenced in section 4.6 have been observed after administration of a double dose of vaccine.

Field studies

One field study was performed to assess the safety of the vaccine. 51 conventional pregnant females of a rabbit breeding farm in France were vaccinated according to the vaccination scheme. All animals were observed for local or systemic reactions during the study. The zootechnical performances were also followed. The field study demonstrates the safety of the vaccine in rabbit's industrial breeding farm in pregnant animals.

Overall, the vaccine proved to be well tolerated in the target species. The results confirm the observations made in the laboratory studies. The local and systemic reactions observed are described in the SPC and package leaflet under "adverse reactions".

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 the risk to the environment from the use of the vaccine is minimal. No warnings in regards to environmental exposure from the use of the vaccine 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.

IV. CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the Ph. Eur. monograph 2325 "Rabbit haemorrhagic disease vaccine (inactivated)" for the classical rabbit haemorrhagic disease virus type 1 (RHDV1).

In the absence of a Ph. Eur. monograph specific to the variant RHDV type2 of lesser virulence (lower mortality observed in the field and during experimental trials), a greater number of rabbits was included in the study to evaluate the protection conferred by the vaccine against the variant RDHV (15 unvaccinated controls/10 vaccines). As the criteria of validity of the immunogenicity test of the Ph. Eur. monograph cannot be applied to the RHDV variant strain, the applicant has provided a statistical analysis to show that there is a significant difference between the vaccines and the controls.

Eight studies were performed in laboratory conditions with the vaccine FILAVAC VHD K C+V.

The efficacy was demonstrated in controlled laboratory challenge studies by infection with classical (RHDV1) and type 2 (RHDV2) virus strains.

All the animals tested were SPF rabbits without antibodies against RHD virus.

The onset of immunity was established based on the results of seven trials in which seronegative rabbits 10 weeks old were vaccinated once by subcutaneous route. Control groups of rabbits were included. All the rabbits were challenged with RHDV1 or RHDV2 strains 7 days after the vaccination. Following the challenge, the mortality in both groups was compared. The results of the different studies are summarised in the table below. The reduction of mortality due to rabbit haemorrhagic disease caused by classical (RHDV1) and type 2 (RHDV2) virus strains was demonstrated.

The duration of immunity was established based on the results of one trial in which 25 SPF rabbits 4 weeks old and 78 SPF rabbits 10 weeks old were vaccinated. Control groups of rabbits were included. The 4 weeks old rabbits were challenged with RHDV1 or RHDV2 strains 12 months after the vaccination. The 10 weeks old rabbits were challenged with RHDV1 or RHDV2 strains at 6, 12 and 18 months after the vaccination.

For rabbits 4 weeks old, the vaccination did not induce a sufficient protection against the RHDV1 strain (less than 90% protection which is required by the Ph. Eur. 2325). A significant reduction of mortality after the challenge with the RHDV2 strain was seen in the vaccinated group compared to the control group. For rabbits 10 weeks old, the vaccination induced a satisfactory protection after a RHDV1 challenge at 6 and 12 months post-vaccination. At 18 months post-vaccination, the protection against the RHDV1 strain was not demonstrated (only 75% controls died instead of 80% which is required by the Ph. Eur. 2325). A significant reduction of mortality after the challenge with the RHDV2 strain was seen in the vaccinated group compared to the control group at 6, 12 and 18 months post-vaccination.

Summary of the efficacy studies

Study	Animals	Vaccine	Challenge Time- strain used	Results Percentage of mortality	Conclusion
1	80 <u>SPF</u> rabbits 10 weeks old G1 : 5C G2 : 15C G3 : 10 V G4 : 10 V	Filavac VHD K C+V	Day 7 post-vaccination RHDV1 strain : G 1, 3 RHDV2: G 2, 4,	RHDV1: G1 : 80% G3 : 0% RHDV2: significant difference G2 : 47% G4 : 0%	Protection against RHDV1 I strain in compliance with Ph. Eur. 2325 Protection against RHDV2 strain : significant reduction of mortality

2	15 <u>SPF</u> rabbits 10 weeks old G1 : 5C G2 : 10V	Filavac VHD K C+V	Day 7 Classical strain	RHDV1: G1 : 60% G2 : 0%	Protection against RHDV1 strain not in compliance with Ph. Eur. 2325: only 60% mortality for controls
3	20 <u>SPF</u> rabbits 10 weeks old G1 : 10C G2 : 10V	Filavac VHD K C+V	Day 7 Classical strain	RHDV1: G1 : 90% G2 : 0%	Protection against RHDV1 strain in compliance with Ph. Eur. 2325
4	25 <u>SPF</u> rabbits 10 weeks old G1 : 15C G2 : 10V	Filavac VHD K C+V	Day 7 Variant strain	RHDV2: significant difference G1 : 47% G2 : 0%	Protection against RHDV2 strain : significant reduction of mortality
5	40 <u>SPF</u> rabbits 10 weeks old G1 : 15C G2 : 5C G5 : 10 V G6 : 10 V	Filavac VHD K C+V	Day 7 Classical strain : G 2 and 6 Variant strain : G 1 and 5	RHDV1: G2 : 100% G6 : 0% RHDV2: significant difference G1 : 47% G5 : 0%	Protection against RHDV1 strain in compliance with Ph. Eur. 2325 Protection against RHDV2 strain : significant reduction of mortality
6	30 <u>SPF</u> rabbits 10 weeks old G1 : 15C G2 : 10 V	Filavac VHD K C+V Half dose	Day 7 Variant strain	RHDV2: significant difference G1 : 40% G5 : 0%	Protection against RHDV2 strain : significant reduction of mortality
7	40 <u>SPF</u> rabbits 10 weeks old G1 : 5C G2 : 10 V	Filavac VHD K C+V	Day 7 Classical strain	RHDV1: G1 : 100% G5 : 0%	Protection against RHDV1 strain in compliance with Ph. Eur. 2325
8	156 <u>SPF</u>	Filavac	6, 12 and 18	RHDV1 - 10	Protection

	rabbits 10 weeks old T10 : 78C V10 : 78V 50 <u>SPF</u> rabbits 4 weeks old T4 : 25C V4 : 25V	VHD K C+V	months for 10 weeks old rabbits 12 months for 4 weeks old rabbits With classical and variant strain	weeks rabbits : 6 months: - C: 100% - V: 10% 12 months: - C: 100% - V: 9% 18 months: - C: 75% - V: 8% RHDV2: significant difference 6 months: - C: 47% - V: 0% 12 months: - C: 69% - V: 0% 18 months: - C: 41% - V: 0%	against RHDV1 strain for 10 weeks old rabbits in compliance with Ph. Eur. 2325 at 6 and 12 months but not at 18 months (only 75% controls died instead of 80%)
				 Mortality 12 months challenge - 4 weeks rabbits: RHDV1 : - C: 100% - V: 23% RHDV2: significant difference - C: 50% - V: 0%	Protection against RHDV2 strain : significant reduction of mortality at 6, 12 and 18 months For rabbits 4 weeks old, Protection against RHDV1 strain not in compliance with Ph. Eur. 2325 (less than 90% protection) Protection against RHDV2 strain : significant reduction of mortality at 12 months

C: control animals

V: vaccines

SPF: Specific Pathogen Free rabbit

Field Trials

No field trial was provided. As the vaccine FILAVAC VHD K C+V is a MUMS product the absence of efficacy study in field conditions is acceptable.

The following conclusions can be drawn from the results of the studies concerning onset and duration of immunity, indications for use and immunisation scheme:

4.2. Indications for use, specifying the target species

For active immunisation of rabbits from 10 weeks of age, to reduce mortality due to rabbit haemorrhagic disease caused by classical (RHDV1) and type 2 (RHDV2) virus strains.

Onset of immunity: 7 days.

Duration of immunity: 1 year.

4.4 Special warnings

No information is available on the use of the vaccine in seropositive animals, including animals with maternally derived antibodies. Thus, in situations where a high level of antibodies is expected, the vaccination scheme must be adjusted accordingly.

The efficacy of the vaccine in animals younger than 10 weeks of age has not been demonstrated.

4.9 Amounts to be administered and administration route

One dose (0.5 ml) per subcutaneous injection per animal.

Primary vaccination: from the 10th week of age.

Revaccination: annually.

Apply usual aseptic conditions.

Shake gently before and occasionally during administration to maintain a homogeneous suspension.

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 veterinary Heads of Agencies website (<http://www.hma.eu/vmrproductindex.html>).

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.

Summary of change (Application number)	Section updated in Module 3	Approval date
variation FR/V/0315/001/IA/001: FILAVIE address modification	None – SPC updated	June 2017
variation FR/V/0315/001/IB/002: Nature and composition of immediate packaging (plastic blister for single dose presentation) – multi-dose presentation: 1 or 14 vials	None – SPC updated	July 2017
variation FR/V/0315/001/II/006/G: Change in the fill weight/fill volume of multidose presentations- Shelf life	Section II – SPC updated	Sept 2019
variation FR/V/0315/001/II/007 and 008: new specifications of RT-PCR quantification	None	Sept 2019
variation FR/V/0315/001/II/009: warning removal for pet rabbits	Section III – SPC updated	Sept 2019