14 July 2016
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for ERAVAC (EMEA/V/C/004239/0000)

Common name: rabbit haemorrhagic disease vaccine (inactivated)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

On 30 September 2015 the applicant Laboratorios Hipra, S.A. submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for ERAVAC, under Article 3(2)(a) of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 4 June 2015 as ERAVAC contains a new active substance (rabbit haemorrhagic disease type 2 virus (RHDV2), strain V-1037 (inactivated) which is not yet authorised as a veterinary medicinal product in the community.

The rapporteur appointed is Cristina Muñoz Madero and the co-rapporteur is Paolo Pasquali.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC. This application has been subject to accelerated assessment, based on the justification that there is a lack of available products against the new variant RHDV2 in Europe which is considered a serious epizootic animal disease and that therefore the product addresses unmet needs and is in the interest of animal health.

ERAVAC is an emulsion for injection in rabbits and the proposed route of administration is subcutaneous use. The product is intended for active immunisation of rabbits to reduce mortality against the new variant of rabbit haemorrhagic disease virus, called RHDV2.

The vaccine contains inactivated RHDV2 strain V-1037 as active substance and is presented in a cardboard box containing one vial of 5 ml of product which is equivalent to 10 doses, or 20 ml of product equivalent to 40 doses.

On 14 July 2016, the CVMP adopted an opinion and CVMP assessment report.

On 22 September 2016, the European Commission adopted a Commission Decision granting the marketing authorisation for ERAVAC.

Scientific advice

The applicant did not seek scientific advice at the CVMP.

MUMS/limited market status

The applicant requested eligibility of this application for minor use minor species (MUMS)/limited market by the CVMP, and the Committee confirmed at their 7 May 2015 meeting that, where appropriate, the data requirements in the relevant CVMP guideline on MUMS/limited market would be applied when assessing the application. MUMS/limited market status was granted as rabbits are considered a minor species.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system (DDPS)

A detailed description of the pharmacovigilance system (dated 02/03/2012) which fulfils the requirements of Directive 2001/82/EC was submitted. Based on the information provided the applicant has services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the European Union (EU) or in a third country.

In addition to the DDPS, a periodic safety update report (PSUR) was submitted covering the period from

10 July 2014 to 31 October 2015 following use in several Member States where the product is permitted for use by national competent authorities under exceptional circumstances.

Manufacturing authorisations and inspection status

ERAVAC is manufactured in the EU by Laboratorios HIPRA, S.A. at two different sites all located in Amer, Girona, Spain. These sites have a manufacturing authorisation issued on 13 May 2014 by Spanish Agency of Medicines and Medical Devices.

The active substance of the vaccine is manufactured by CIAMER, the antigen manufacturing site of Laboratorios HIPRA, which is located in Carretera Santa Coloma Farners pK21.6, Amer, 17170 Girona, Spain.

The manufacture of the vaccine (blending, filling and labelling) as well as the in-process control tests and the control tests on the finished product, including the batch release of the product, are carried out by Laboratorios HIPRA, in the manufacturing site located in Aver, La Selva 135, Girona, Spain.

Quality control of thiomersal is carried out in an outsourced laboratory.

Good Manufacturing Practice (GMP) certificates, which confirm the date of the last inspection and shows that the sites are authorised for the manufacture and batch release of such veterinary dosage forms, have been provided.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certifications of the manufacturing sites were considered in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as emulsion for injection containing inactivated strain V-1037 of RHDV2 as active substance. The potency of the vaccine per dose (0.5 ml) is expressed as a minimum 70% of vaccinated rabbits giving a cELISA (competitive enzyme-linked immunosorbent assay) serological titre ≥40 ELISA Units. The product contains thiomersal as preservative and mineral oil as adjuvant. The emulsion is prepared with sorbitan-mono-oleate and polysorbate 80. Other ingredients are listed as excipients in section 6.1 of the SPC. The excipients are compliant with European Pharmacopoeia (Ph. Eur.) standard, where applicable.

Container

The container is a colourless glass multidose vial, rubber stopper and aluminium capsule of 5 ml (10 doses) and 20 ml (40 doses). Glass vials are of Ph. Eur. type I standard and the rubber stoppers are of Ph. Eur. type I, nitrile chlorobutyl.

Details of the sterilisation methods for the glass containers and rubber stoppers have been provided. Certificates of analysis for the vials, rubber stoppers, and aluminium caps from the respective manufacturers were submitted, including the outlines.

The antigen is stored in polyethylene bags. Certificate of analysis of these bags, including certificate of irradiation, is provided.

Development pharmaceutics

An explanation and justification for the composition and presentation of the vaccine was provided.

Choice of the vaccine strain

The “classic form” of rabbit haemorrhagic disease (RHD), is known in Europe since the late 1980s. The rabbit haemorrhagic disease virus (RHDV) affects domestic and wild rabbits. Up to now, the disease is well controlled by vaccination with the currently available vaccines. One RHDV serotype is currently known, including the antigenic variant RHDVa, the classical variant.

In 2010, first in France and then elsewhere in Europe, RHD outbreaks appeared in vaccinated rabbits. Despite that the observed macroscopic lesions were consistent with RHD, there were some differences when compared to the classical form of the disease, as follows:

– Lower virulence

– Course of the disease slightly prolonged

– Lower and highly variable mortality rates

– Deaths occurred later and over a longer period

– Disease becomes chronic or subacute more frequently

– Higher mortality in young rabbits than adults

On the basis of the differences in symptoms in comparison to the classical form of the disease, it is called “new variant” of the RHD, hence, a new variant of RHDV. In literature, the new variant of the virus is called RHDV2 or RHDVb. In this procedure, RHDV2 is used.

RHDV is subdivided in six genogroups but, more recently, a new RHDV variant with a unique genetic and antigenic profile has emerged and typical genogroups of classical RHDV are being replaced by this new variant (Lopes et al. *Viruses 2015, 7, 27–36)*.

From literature (Lopes et al, *Viruses 2015, 7, 27–36,* Wescott et al., *Veterinary Record March 29, 2014,* Le Gall-Reculé et al. *Veterinary Research 2013 44:81)* it can be concluded that current vaccines, containing classical RHDV strains, do not protect rabbits from the new variant (from partial protection to no protection).

The RHDV2 is a non-enveloped single-stranded positive-sense RNA virus that belongs to the genus *Lagovirus*, *Caliciviridae* family. Phylogenetic trees published by different authors (Le Gall-Reculé et al., Abrantes et al., Dalton et al., Lopes et al.) support the emergence of a new branch highly differentiated.

According to the applicant, the age of the affected animals and the lower mortality rate are the main characteristics to take into account when choosing the vaccine strain.

The vaccine strain chosen for ERAVAC was isolated in Spain from a macerated liver of a fattening rabbit with lesions compatible with a virulent RDHV2. To confirm that the strain belongs to the new variant, the Spanish National Reference Laboratory (LCV) that is located in Algete, Madrid, Spain, carried out a real-time RT-PCR on the macerate. This specific RT-PCR has been developed by the Spanish National Reference Laboratory and the description and the validation of the method is provided in a draft paper that will be published shortly. The Central Veterinary Laboratory has certified that original virus from HIPRA belongs to the new variant. The isolate was coded as V-1037 and was transferred from LCV to Laboratorios HIPRA, S.A.

RHDV2 is only able to grow in live infected rabbits and the virus is recovered from their livers and spleens when they have succumbed to the infection or are euthanized. In line with the 3Rs principles, the applicant attempted to replicate the virus in different cells lines without success.

Reasonable justification is given regarding the relevance of the chosen vaccine strain within the EU.

Other ingredients

The adjuvant chosen in this inactivated vaccine is mineral oil. Polysorbate-80 and sorbitan mono-oleate are the other required excipients to form the emulsion. Thiomersal is used as preservative. The main dilution medium used in this vaccine is phosphate buffer solution (PBS).

The formulation of batches used during the pivotal clinical studies was the final formulation.

The efficacy of the thiomersal was satisfactorily demonstrated in accordance with Ph. Eur. 5.1.3 and Monograph 0062.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC

Product development

The virus is grown *in vivo* in the livers and spleens of rabbits and therefore it is considered justified to use some antibiotics in the early stages of production of the vaccine (in compliance with Ph. Eur. 0062). The consumer safety implications arising from the potential presence in the finished product of the antibiotics used in production are addressed. The antibiotic substances appear in table 1 of the annex to Commission Regulation (EU) 37/2010. The remaining levels of these antibiotics are in compliance with their approved MRLs for rabbits allowing the conclusion that the amount of antibiotics per dose can be considered as traces only.

The potential impact on the development of resistance in the smallest rabbits (dwarf rabbits with a weight of 500 g) is addressed and it can be concluded that the amount of the antibiotics in finished product do not reach levels that would be expected to lead to the development of antibiotic resistance in vaccinated rabbits.

The residual live virus control (inactivation control) is carried out on each single harvest of antigen immediately after inactivation in compliance with Ph. Eur. 0062.

Method of manufacture

The master seed virus (MSV) was obtained from the original virus stock by a passage in live rabbits: the original virus is inoculated in SPF rabbits and, when animals died or are euthanized, livers and spleens are removed to obtain a macerate. This macerate was treated with PBS and antibiotics, and then, mixed with glycerol at 10%. It was coded as VMS-RHD-V-1037 and it is stored frozen at -80 ºC. Identity, purity (by sequencing the VP60 gene) and extraneous agents testing are controlled in line with requirements of Ph. Eur. monograph 0062 on vaccines for veterinary use.

The working seed virus (WSV) is obtained from the MSV as described before. Controls carried out on WSV are: titre and bacterial and fungal sterility.

The production of the vaccine is performed in two phases: the production of the antigen and the production of the finished product (vaccine blending). Each stage of the process takes place under environmental conditions according to GMP. The manufacturing process of the antigen is based on the “seed lot system”. The viral harvest is obtained from liver and spleen tissues which are homogenized and inactivated by adding binary ethyleneimine (BEI). The inactivated harvest is clarified and filtrated

through sterilizing filters. The antigen is filled into sterile single use bags. A stability report of the antigen is provided.

The final vaccine is obtained by mixing the oily phase with the aqueous phase (containing the antigen) to obtain an emulsion.

The inactivation process is described in detail and the inactivation kinetics for the antigen is provided and is in line with requirements of Ph. Eur. 0062.

The method of manufacture is satisfactorily described and the different steps provide enough information according to Directive 2001/82/EC.

In-process control tests are considered in line with the requirement of current guidelines.

Control of starting materials

Active substance

Inactivated RHDV2 strain V-1037 is the active substance of the vaccine.

This new variant of the RHDV is called RHDV2.The RHDV was isolated in August 2013 from a liver macerated obtained from an outbreak where infected rabbits showed typical lesions of RHDV2 disease in La Rioja (Spain).

The MSV was obtained at HIPRA facilities from the original virus stock. Controls on MSV were carried out and a certificate of analysis is provided. Titre of MSV (and WSV) is performed by determination of haemagglutinant units (HAU) and the procedure is adequately described.

Identity and purity controls of the MSV were carried out by sequencing of the VP60 gene of the virus, confirming that the vaccine is RHDV2. Bacterial and fungal sterility, absence of mycoplasma and absence of extraneous agents controls were performed with satisfactory results.

Starting materials of biological origin not listed in a pharmacopoeia

Healthy adult purpose bred rabbits are used in the production of the vaccines. Rabbits are free from myxomatosis and RHD and regularly monitored for the absence of various virus, bacteria and ecto- and endoparasites. Certificates of analysis including the qualifications and procedures used are provided for each supplier farm.

The controls applied on raw materials guarantee sterility of the vaccine and absence of introduction of extraneous agents.

Excipients

Sorbitan-mono-oleate and Polysorbate 80 are used to obtain the emulsion. Mineral oil is used as adjuvant and thiomersal is added as preservative. PBS is used during the manufacture process as diluent in different steps.

For all materials used, relevant certificates of analysis are provided. The specifications are included in the certificates and they are in accordance with the requirements of the monographs.

The routine controls for all the starting materials are considered appropriate.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The strain used in the product was isolated from a macerated rabbit liver. The propagation of the virus during the manufacture of the vaccine is performed on rabbits.

Rabbits are a non TSE-relevant animal species according to the Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) and no other ingredients of animal origin are used during the manufacturing process. It is concluded that the risk of transmitting transmissible spongiform encephalopathy (TSE) infectivity through the use of this vaccine is negligible.

Control tests during production

Control tests during production include: titre, identity, residual live virus (inactivation test), residual thiosulphate, pH, bacterial and fungal sterility, integrity of filters, appearance of the emulsion and volume verification. Validation studies of titration, residual live virus and residual thiosulphate have been provided.

Overall, the in-process control tests for the production of the vaccine can be considered satisfactory. The identity control is able to differentiate the classical from the new variant of the virus.

Rabbits used for the production of the vaccine are also controlled.

The in-process tests are deemed to be sufficient to control all the critical steps in the manufacturing.

Control tests on the finished product

On each batch, control tests carried out include appearance, concentration of thiomersal, viscosity, weight per millilitre, potency test and identity test. After filling, control of appearance, sterility and volume control are performed.

The identification and quantification of antibodies against RHDV2 in serum samples of rabbits vaccinated with ERAVAC is carried out by means of a competitive ELISA developed by the IZSLER (OIE RHDV Reference Laboratory). Validation of this method set up at HIPRA facilities is provided.

The tests on the finished product are well described.

Batch potency test

Rabbits were challenged at 7 days post vaccination and a reduction of the mortality was observed. Nevertheless, the proposed batch potency test (BPT) is based on the serological response at 14 days post vaccination because the serological response at 7 days post vaccination does not show significant differences between rabbits vaccinated with standard or sub-standard dose. So, it would not be possible to discriminate sub-standard batches. As the CVMP Reflection paper on control of the active substance in the finished product for immunological veterinary medicinal products (EMA/CVMP/IWP/582970/2009) suggests, if there is a good dose-response relationship, and a significant difference can be shown between a standard batch and a batch with, for example, half the amount of antigen (thus making possible the detection of a defective batch containing only 50% of antigen), the efficacy of a batch containing half the amount of antigen should be considered. According to this, it is shown that at 14 days post vaccination there is a statistically significant difference when the cut-off is established in 40 cELISA Units between rabbits vaccinated with standard dose or sub-standard dose.

In brief, batches can be released if:

- All rabbits are seronegative at day 0 (cELISA Units lower than 10)
- Control rabbits remain seronegative at day 14
- More than 70% of vaccinated rabbits show a titre equal or more than 40 cELISA Units.

A validation of the BPT was provided and it can be considered correct, the establishment of the BPT was supported by acceptable criteria.

Consistency batches

Manufacturer Batch Protocols with all control tests (in-process and finished product) on 3 batches are provided.

The results from control tests are compliant with Ph. Eur. monographs and include all the required controls for the product.

Stability

Regarding the stability of the antigen, results of testing titre, pH and sterility on two batches from T0 till T12 months have been provided with satisfactory results. Another antigen batch has been tested during 9 months, also with satisfactory results. The stability of the antigen, stored in polyethylene sterile bags at 2–8 ºC can be established at 12 months.

The applicant has provided results of stability studies carried out on two batches of vaccine, both of them manufactured from the same final bulk. This is acceptable according to the CVMP 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).

The stability of the vaccine stored in the final containers at 2–8 ºC protected from light, was established at 1 year.

A full protocol of batches was provided giving the results for all tests performed during production and on the finished product

On the basis of the data provided in the dossier, the in-use stability of the vaccine is established as “Use immediately”.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner.

The manufacturing process for the vaccine is described in detail. A validation study was provided for inactivation kinetics which can be considered as appropriately validated. A table of blending is provided and the batch size of final product is adequately established.

Starting materials used in the production of the vaccine are satisfactorily described and in compliance with the requirements of Ph. Eur. Starting materials not listed in a pharmacopoeia and in-house media are also described including relevant and acceptable control tests.

The method to characterise the virus and its validation are described and acceptable. The Central Veterinary Laboratory in Algete (Madrid, Spain) has certified that original virus from HIPRA belongs to the new variant.

Production and testing of the MSV and WSV are clearly described. SOPs have been provided describing all testing, in addition to some validation reports. Identity of the vaccine strain has been performed at HIPRA by sequencing of the VP60 gene.

Taking into account the method of production of the vaccine, in live rabbits, additional control tests on more extraneous agents than those provided are performed and therefore concrete specifications on rabbits for production are provided.

The risk of TSE infectivity through the use of this vaccine is negligible.

The in-process tests for the vaccine are described satisfactorily and validation of the titration method, detection method of myxoma virus in the RHDV2 MSV, sterility control, determination of thiomersal, residual live virus method and control of residual thiosulphate method have been provided.

The finished product tests for the vaccine are described satisfactorily. The criteria established in the proposed batch potency test are considered acceptable and validated with respect the efficacy of the vaccine.

The results of the analysis of three batches indicate satisfactory consistency between batches.

Stability of the antigen has been established at 12 months. The shelf life of the veterinary medicinal product as packaged for sale can be established in one year. The vaccine, after the first opening, should be used immediately.

Part 3 – Safety

Laboratory tests

Safety of the administration of one dose

The safety of one dose of the vaccine was assessed in a laboratory trial with 20 animals monitored for up to day 14 post vaccination. Local and/or systemic reactions were recorded if presented and the rectal temperature of the rabbits was recorded daily from the day before vaccination, on the day of vaccination, four hours post vaccination and then daily for 6 days.

The study was designed, where possible, according to the requirements described in the current Ph. Eur. monograph 2325 “Rabbit haemorrhagic disease vaccine (inactivated)” although this monograph is described for the classic RHDV and not for the new variant.

The main differences in study design are related to the different age of the animals used in the studies and the percentage of mortality considered, as the new variant affects to younger animals and presents lower mortality rates. This is considered acceptable.

In addition, the recommendations stated in Ph. Eur. 5.2.6: Evaluation of safety of veterinary vaccines and immunosera, and CVMP Guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets (EMA/ CVMP/IWP/123243/2006) were also considered.

The study was conducted in a group of 20 rabbits of the minimum age recommended for vaccination (1 month). The rabbits were free from antibodies against RHDV and RHDV2.

- The rabbits were vaccinated according to the established vaccination plan with a single 0.5 ml dose by subcutaneous (SC) route. Local and/or systemic reactions were recorded if present and the rectal temperature of the rabbits was recorded.
- In the results obtained none of the animals showed general clinical signs throughout the 14 days

observation period.

- The rectal temperature of the animals was taken on the day before vaccination, on the day of vaccination, 4 hours post vaccination and daily for 6 days. Before vaccination, the baseline temperature of all the rabbits was below 40 °C. After vaccination, specifically 2 and 3 days post vaccination, all the animals suffered a slight increase in rectal temperature which in no case exceeded 40.5 °C. Furthermore, the maximum increase in temperature observed was 1.29 °C. On day 4 post vaccination two animals had a rectal temperature slightly above 40 °C but all animals were within normal parameters on day 5 post vaccination and until day 6 post vaccination.
- Results from all animals met the requirements of the Ph. Eur. No animal showed an increase of more than 2 °C rectal temperature and the average increase of the group did not exceed 1.5 °C

In view of these results, it is concluded that the information for a very common adverse reaction should be included in the SPC concerning a transient temperature increase slightly above 40 °C that might occur within two or three days following vaccination and that resolves spontaneously without treatment, by day 5 post vaccination.

To conclude, the results indicate that vaccination with one dose of the product is generally well tolerated.

Concerning the vaccine batch used, a standard batch was used in agreement with the reduction in data requirements for MUMS/limited market products as stated in CVMP Guideline EMA/CVMP/IWP/123243/2006.

As this is classified as a MUMS/ limited market indication, no maximum dose potency has been studied in the safety studies presented and as the antigen is inactivated, no overdose studies would be required.

Safety of one administration of an overdose

According to Directive 2001/82/EC, overdose testing is required only for live immunological veterinary medicinal products. Therefore, an overdose safety study has not been conducted for the product, and this is acceptable.

Safety of the repeated administration of one dose

The safety of one repeated administration of a single dose of the product was not investigated considering that the vaccine is intended to be administered only once. This is acceptable.

Examination of reproductive performance

No study has been carried out to assess the safety in pregnant or lactating rabbits and this is addressed in the SPC.

Examination of immunological functions

Studies on the effect of the product on immunological performance were not provided.

Taking into consideration the nature and composition of the vaccine, there is no reason for suspecting an impairment of the immune system under the claimed conditions of use of the vaccine. The lack of studies is considered acceptable.

Study of residues

Concerning residues, no specific study of residues has been carried out. The active substance is a principle of biological origin intended to produce active immunity and it is not within the scope of Regulation (EC) No 470/2009. The other components of the vaccine are either allowed substances for which table 1 of the annex to the Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this veterinary medicinal product.

Two antibiotic substances are used during the production process it was demonstrated that the residual amounts of these components in the finished product would not lead to residue levels in food above approved and established MRLs. Adequate calculations and justifications were submitted.

The proposed withdrawal period of zero days is acceptable.

Interactions

No data were provided to investigate interactions of the vaccine with other veterinary immunological products and therefore an appropriate statement in the SPC is required that no information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal products.

Field studies

According to the CVMP 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), if laboratory studies are sufficient not to raise a safety concern, field studies are not required.

As the laboratory safety study presented has adequately demonstrated safety of the vaccine and only a slight increase in rectal temperature was observed, no further studies to demonstrate safety are deemed necessary.

Also the previous use of the vaccine in some European countries and the absence of reports for suspected adverse reactions has been taken into account.

User safety

A user safety risk assessment conducted in accordance with the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1) was provided.

The vaccine, to be administered by SC injection, contains an inactivated active substance not expected to pose a risk for the user.

Other ingredients included in the formulation of ERAVAC are mineral oil, sorbitan mono-oleate, polysorbate 80, thiomersal and PBS (phosphate buffer solution). At relevant levels, no local or systemic harmful effects for human beings have been reported for these components except for mineral oil. Mineral oil is known to cause severe pain and swelling, particularly if injected into a joint or finger. Therefore, an appropriate standard warning is included in the SPC. Apart from this, all the components of the vaccine are common excipients already authorised in other veterinary vaccines.

The most relevant route of user exposure is considered to be accidental self-injection. However, it is considered that the probability of accidental self-injection is very low and that the probability that the user would self-inject the whole vaccine dose is negligible.

Overall it is concluded that the user safety for this product is acceptable when used as recommended in the SPC.

Environmental risk assessment

An environmental risk assessment has been provided in accordance with the Note for guidance on the environmental risk assessment of immunological veterinary medicinal products (EMEA/CVMP/074/95).

1. Hazard identification

- The vaccine is administered by the SC route to individual rabbits.
- The active ingredient is an inactivated antigen corresponding to RHDV2, with mineral oil as adjuvant and sorbitan mono-oleate, polysorbate 80, thiomersal and PBS as excipients.

2. Exposure to hazard

- None of the vaccine components are metabolised or excreted to the environment.
- The quality of packaging materials complies with the requirements of Ph. Eur.
- There is a very minimal risk of environmental exposure to the vaccine and the consequences would be negligible even if this did occur.

The impact of RHDV2 infection on wild rabbits and hares because of their importance in the survival of other endangered predator species, up to now, the Iberian imperial eagle (*Aquila adalberti*) and the Iberian lynx (*Lynx pardinus*) has been taken into account by Dalton et al. 2014.

Based on the data provided the ERA can stop at Phase I. ERAVAC is expected to pose a negligible risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The safety of the vaccine has been assessed in one GLP laboratory study. It was assessed in 20 animals of the minimum age and free from antibodies and, for a period up to day 14 post vaccination. Local and/or systemic reactions and temperature were recorded.

A transient temperature increase below 2 °C was observed between two or three days following vaccination which resolved spontaneously without treatment by day 5 post vaccination. This point is appropriately reflected in the SPC.

As two antibiotic substances are used during the production process, the applicant has demonstrated that the possible residual amounts of these components in the finished product are in compliance with the approved MRLs for the target species. A withdrawal period of zero days is acceptable.

The user safety for this product is acceptable when used as recommended. Due to the type of adjuvants included in the vaccine (mineral oil) in the case of self-injection the user should seek for medical advice immediately as reflected in the SPC.

Based on the data provided the ERA can stop at phase I. The vaccine is not expected to pose a risk to the environment when used according to the SPC.

Part 4 – Efficacy

Introduction and general requirements

Five laboratory studies were submitted to support the efficacy of ERAVAC as indicated in the table below.

Efficacy requirements	Route / Species /Age at Vaccination
Establishment of a challenge model (challenge strains V-1032 and V-1035)	Intramuscular / rabbits / not vaccinated 40 rabbits challenged with 2 different strains at 35/60 days
Dose determination and onset of immunity (OOI) (thiomersal as preservative)	Subcutaneous / rabbits / 28–30 days 40 vaccinated; 20 placebo
Dose Determination (thiomersal as preservative)	Subcutaneous / rabbits / 2 months 28 vaccinated; 14 placebo
OOI and minimum protective dose (benzyl alcohol as preservative)	Subcutaneous / rabbits / 28 days 116 vaccinated; 56 placebo
Study on the influence of maternally derived antibodies (MDA) on vaccine efficacy in rabbits	Subcutaneous / rabbits / 30 days 40 vaccinated; 20 placebo

The above studies have been carried out in accordance with the general principles and requirements of Directive 2001/82/EC, the current version of the monograph no. 5.2.7. of the Ph. Eur. Evaluation of efficacy of veterinary vaccines and immunosera and, whenever possible, monograph 2325 of the Ph. Eur. Rabbit haemorrhagic disease vaccine.

The efficacy studies have been performed also in line with the specific CVMP Guideline concerning MUMS/ limited market data requirements (EMA/CVMP/IWP/123243/2006-Rev.2) and reductions in data requirements have been taken into account for the assessment of this vaccine.

Laboratory trials

Five laboratory trials were carried out to investigate the efficacy of the vaccine.

Establishment of a challenge model (challenge strains V-1032 and V-1035)

A study was carried out to assess the mortality rates of two different pathogenic field strains of the new variant RHDV2 to determine the most suitable strain to be used as challenge strain.

Two challenge strains were used. One of the strains used in the study, strain V-1032, was demonstrated to be a mixture of the new variant RHDV2 and the classical RHDV by a PCR test. Challenge strain V-1035 was isolated from the liver of 28-day-old rabbits that died during an outbreak of RHDV2 in Spain by the diagnostic centre of Laboratorios Hipra (Diagnos) in 2012. This field strain is representative of the strains currently circulating in the EU. Strain V-1035 was chosen for the challenge studies on the basis of the related mortality rate, the high virus titration in the liver and serology results. The pattern was compatible with RDHV2. The challenge strain was fully characterised as RHDV2 by means of RT-PCR (by sequencing the VP60 gene).

The challenge was administered by intramuscular route which is widely used in the published literature to perform experimental infections with the classic form of the disease and also for RHDV2.

The challenge was used in three of the four laboratory studies. In one of those studies challenge was performed 7 days post vaccination and in another one rabbits were challenged 7 and 14 days post vaccination, depending on the group. In a third study animals were challenged 14 days post vaccination. Challenge strain V-1035 was used in these studies.

Onset of immunity

The studies for determination of vaccine dose and OOI, and minimum protective dose, were planned to support the efficacy claims.

In one study, results show that the vaccine was effective to protect vaccinated rabbits against strain V-1035 7 days after vaccination. Survival of the vaccinated was at 100%, whereas survival of the controls was at 37%. These results met the efficacy parameters established for this efficacy study: i.e. for more than 87.5% of vaccinated animals to show no symptoms of RHD.

In the second study survival of vaccinated rabbits was 93% compared with 50% for rabbits given placebo, that were challenged 7 days after vaccination.

Therefore, results demonstrate that the OOI is established from 7 days post vaccination to reduce mortality and this has been reflected in the SPC.

To determine the vaccine dose, two studies are provided: one dose response challenge study and one dose response serology study.

In the first study one-month old animals were vaccinated (inactivated RHDV2 strain, V-1037, and thiomersal as preservative) and challenged with V-1035, with the aim to investigate dose determination and OOI. As indicated before, the results demonstrate efficacy of the vaccine.

A dose response study based on seroconversion was provided. The study was carried out with two-months-old animals.

The results obtained in this study show that the administration of one dose of the inactivated vaccine containing either 2^8 HAU/50 µl (substandard dose) or 2^9 HAU/50 µl (standard dose) of the RHDV2 strain V-1037 is capable of inducing high levels of anti-RHDV2 antibodies in comparison with unvaccinated control rabbits. The serological response quantified by a specific competition ELISA (cELISA) can be observed seven days after vaccination and increases progressively up to end of the study (21 days).

Overall data showed that the product is effective for the active immunisation of rabbits from the age of 30 days to reduce mortality caused by the new variant of rabbit haemorrhagic disease virus (RHDV2) after challenge with the strain V-1035.

The OOI is 7 days.

Duration of immunity (DOI)

The DOI has not been established. On the basis of serological data, antibodies are present 21 days post vaccination.

According to Annex I to Directive 2001/82/EC it is stated that, "*unless justified, the onset and duration of immunity shall be established and supported by data from trials"*. In this application specific laboratory trials have been conducted to establish the onset of immunity.

A specific laboratory study has not been conducted to establish the duration of immunity through a conventional vaccination and challenge experiment. Furthermore there are no specific field efficacy studies to establish the DOI. However the vaccine has been widely used under special circumstances in some Member States, providing supportive evidence for its efficacy under field conditions, considering that no lack of efficacy reports have been received.

The CVMP accepted the following justification for the omission of such studies on the following basis:

- RHDV2 affects mainly young rabbits and the fattening period is up to 2–3 months in those Member States that are major producers of rabbit meat. The disease is mostly observed in rabbits less than 2 months of age and therefore the efficacy data provided would support protection through the

major risk period when used as recommended for fattening rabbits (Dalton, 2014).

- Data to show the presence of antibodies 21 days after vaccination has been provided in one study. Information to substantiate a correlation between antibody levels (following with the classical strain) and protection has been provided (Zheng T & Parkes JP. Rabbit haemorrhagic disease: advantages of cELISA in assessing immunity in wild rabbits (*Oryctolagus cuniculus*) Vet Microbiol. 2011 15;153(3–4)). Therefore the serological data is supportive of the efficacy of the vaccine through the risk period.
- In the absence of a conventional vaccination and challenge study for DOI, serological data are considered acceptable for this application on the basis of the rationale explained above and taking into account the recommendations limiting the use of the product to fattening rabbits only and where RHDV2 is relevant.
- The vaccine has been used in fattening rabbits for the last 2 years in some Member States. During this time no cases of lack of efficacy have been reported through the pharmacovigilance systems. This performance of the product in Member States therefore indirectly supports the efficacy under field conditions.

In addition, the Committee considered the following aspects related to availability of relevant alternative products:

- There is at present a lack of available products against the new variant RHDV2 in Europe which is considered a serious epizootic animal disease and that therefore the product addresses an unmet need to protect fattening rabbits against a serious infectious disease for which existing vaccines lack adequate protection, and is therefore in the interest of animal health.

The CVMP recommends, however, that the DOI is further established by an appropriate study.

Maternally derived antibodies (MDA)

The efficacy of the vaccine against the new variant RHDV2 in the presence of MDAs is demonstrated.

The vaccine has been shown to protect vaccinated animals with and without MDAs by obtaining 100% survival rates after challenge at 14 days post vaccination. Differences between the control and vaccinated groups were statistically significant.

The studies have been performed in 1-month old animals intended for meat production (fattening rabbits).Safety and efficacy data of the vaccine in, breeding rabbits and pet rabbits, are not available, and therefore only the category of rabbits intended for meat production is considered acceptable in the indication for use.

Field trials

According to the CVMP Guideline on data requirements of immunological veterinary medicinal products intended for minor use or minor species / limited markets (EMA/CVMP/IWP/123243/2006-Rev.2), no field studies have been performed.

Data from the use of the vaccine in Spain, Portugal and Belgium have been also included as support of the safety and efficacy of the vaccine in the field.

Overall conclusion on efficacy

The efficacy of the vaccine was investigated in 5 laboratory studies.

The efficacy of the vaccine has been demonstrated by the results of the laboratory tests for fattening

rabbits (rabbits intended for meat production).

The studies have been performed in 1-month-old vaccinated animals, so the target species should be considered rabbits (for meat production). Safety and efficacy data of the vaccine in breeding rabbits and pet rabbits, are not available, and therefore only the category of rabbits intended for meat production (for meat production) is considered acceptable in the indication for use.

The efficacy of the vaccine was investigated in rabbits under laboratory conditions using an adequate challenge model, including a challenge strain different from the one included in the vaccine.

Studies provided demonstrated that the OOI can be established at 7 days after vaccination (for the reduction of mortality), based on results.

Overall data showed that the product is effective for the active immunisation of rabbits from 30 days of age to reduce the mortality after challenge.

The dose response study based on seroconversion was carried out with two months old animals and this is acceptable.

In one study vaccinated animals with and without MDAs were protected after vaccination by obtaining 100% survival rates after challenge at 14 days post vaccination. Differences between the control and vaccinated groups were statistically significant.

DOI has not been established and this is acceptable taking account of the justification for the absence of such data.

In addition, the applicant is recommended to provide the following information post-authorisation:

The DOI of ERAVAC should be further established by an appropriate study in the appropriate category of target species.

Part 5 – Benefit-risk assessment

Introduction

ERAVAC is an inactivated vaccine intended for the active immunisation of rabbits to reduce mortality caused by the new variant of RHDV (RHDV2). The active substance is the inactivated strain V-1037 of RHDV2. Mineral oil has been used as adjuvant and thiomersal has been used as preservative. The antigen is considered new active substances not previously authorised within EU and is therefore considered a new active substance.

The effective dose of the vaccine has been confirmed. The potency of active substance per dose of 0.5 ml is expressed as a minimum 70% of vaccinated rabbits giving cELISA antibody titres equal or higher than 40 ELISA Units. The vaccine is presented as an emulsion for injection to be administered by SC route in rabbits of minimum 30 days.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application) and has been subject to accelerated assessment.

The product has been classified as MUMS/limited market and therefore reduced data requirements apply that have been considered in the assessment.

Benefit assessment

Direct therapeutic benefit

The therapeutic benefit of ERAVAC is its efficacy in active immunisation of rabbits to reduce mortality caused by RHDV2, which was investigated in five (5) well-designed laboratory studies conducted to an acceptable standard. The vaccine provides protection only against RHDV2, cross protection against classical RHDV is not demonstrated.

The efficacy is demonstrated in fattening rabbits (rabbits used for meat production). No information is available on the efficacy in other categories of rabbits (pet rabbits; rabbits for reproduction) and this is addressed in the SPC.

The OOI is 7 days.

The DOI has not been fully established, which has been justified.

No specific field study is performed but data from the use of the vaccine in the field was included as a support of the efficacy of the vaccine.

Additional benefits

ERAVAC provides a possibility for prophylaxis of RHD, caused by RHDV2, for a minor species.

The product addresses an unmet need to protect fattening rabbits against a serious infectious disease for which existing vaccines lack adequate protection, and is therefore in the interest of animal health.

Risk assessment

Main potential risks:

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety:

For the target animal

Administration of ERAVAC in accordance with SPC recommendations is generally well tolerated in the target animal. The main reported adverse reaction is a slight transient increase in rectal temperature which resolves spontaneously without treatment.

For the user

ERAVAC contains mineral oil which is known to cause serious adverse effects for the user in case of an accidental injection/self-injection. The user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment

The product is not expected to pose any risk to the environment when used as recommended.

For the consumer

The product is not considered to pose a risk to the consumer when used as recommended. Residue studies are not required.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target species, the user, the consumer and the environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for active immunisation of fattening rabbits against the new variant of RHDV2.

The DOI has not been established and this is acceptable as it has been justified on the basis of the reasons discussed before. This information has been included in the SPC.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have satisfactory and uniform performance in clinical use. It is well tolerated by the target animals (fattening rabbits) and presents an acceptable risk for users, consumers and the environment, when used as recommended.
Appropriate precautionary measures, including information in relation to the withdrawal period (set at zero days) have been included in the SPC and other product information.

The overall benefit-risk evaluation for the product is positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the applicant for ERAVAC is since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore recommends the granting of the marketing authorisation for the above mentioned medicinal product.