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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for ERAVAC (EMEA/V/C/004239/II/0003/G)

Common name: rabbit haemorrhagic disease vaccine (inactivated)

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

Rapporteur: Cristina Muñoz Madero

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5545
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

1.1. Submission of the variation application

In accordance with Article 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Laboratorios Hipra, S.A. (the applicant), submitted to the European Medicines Agency (the Agency) on 25 August 2017 an application for a grouped type II variation for ERAVAC.

1.2. Scope of the variation

Scope of the variation application (according to Commission Regulation (EC) No 1234/2008):
C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one

to amend the duration of immunity and demonstrate safety in pet (dwarf) and pregnant rabbits.

Variation details:

Present SPC situation	**Proposed change**
4.2 Indications for use, specifying the target species For active immunisation of fattening rabbits from the age of 30 days to reduce mortality caused by the rabbit haemorrhagic disease type 2 virus (RHDV2) Onset of immunity: 7 days Duration of immunity: has not been established **4.4 Special warnings for each target species** The vaccine provides protection only against RHDV2, cross protection against classical RHDV has not been demonstrated Vaccinate only fattening rabbits No information is available on the safety and efficacy in other categories such as breeding or pet rabbits	**4.2 Indications for use, specifying the target species** For active immunisation of rabbits from the age of 30 days to reduce mortality caused by the rabbit haemorrhagic disease type 2 virus (RHDV2) Onset of immunity: 1 week Duration of immunity: 1 year **4.4 Special warnings for each target species** The vaccine provides protection only against RHDV2, cross protection against classical RHDV has not been demonstrated Vaccinate healthy animals only

4.5 Special precautions for use Vaccinate only healthy rabbits Vaccination is recommended where RHDV2 is epidemiologically relevant	**4.5 Special precautions for use in animals** Vaccination is recommended where RHDV2 is epidemiologically relevant
4.6 Adverse reactions (frequency and seriousness) Very common: a transient temperature increase slightly above 40 ºC might occur between two or three days following vaccination. This slight temperature resolves spontaneously without treatment by day 5 post-vaccination	**4.6 Adverse reactions (frequency and seriousness)** Very common: a transient temperature increase slightly above 40 ºC might occur between two or three days following vaccination. This slight temperature resolves spontaneously without treatment by day 5 post-vaccination Common: slight swelling at the injection site, which may last 24 hours. This local reaction gradually reduces and disappears without need for treatment
(Frequency of adverse reactions as described in QRD)	*(Frequency of adverse reactions as described in QRD)*
4.7 Use during pregnancy, lactation or lay Pregnancy and lactation: Do not use during pregnancy or lactation	**4.7 Use during pregnancy, lactation or lay** Pregnancy Can be used during pregnancy:
4.9 Amounts to be administered and administration route Subcutaneous use Administer 1 dose (0.5 ml) of the veterinary medicinal product to rabbits at the age of 30 days by subcutaneous injection in the lateral thoracic wall	**4.9 Amounts to be administered and administration route** Subcutaneous use Administer 1 dose (0.5 ml) of the veterinary medicinal product to rabbits from the age of 30 days by subcutaneous injection in the lateral thoracic wall. Revaccinate annually.

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 3 and Part 4

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

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

2. Scientific Overview

ERAVAC is an inactivated viral vaccine that contains rabbit haemorrhagic disease type 2 virus (RHDV2), strain V-1037. The product contains thiomersal as preservative and mineral oil (Marcol 52) as adjuvant. The emulsion is prepared with sorbitan-mono-oleate and polysorbate 80. The potency of the vaccine is expressed as a minimum 70% of vaccinated rabbits giving a cELISA serological titre ≥40 ELISA units.

Since only safety and efficacy studies on fattening rabbits were performed in the initial procedure and no information was available on the safety and efficacy in other categories such as breeding or pet rabbits, only fattening rabbits from the age of 30 days were including as target species in section 4.2 of the SPC.

The applicant seeks approval for a type II variation for ERAVAC to demonstrate safety in pet (dwarf) and pregnant rabbits as well as the establishment of the duration of immunity in one year.

2.1. Safety

The applicant has provided two safety studies which have been performed in accordance with the European Pharmacopoeia (Ph. Eur.) monographs 50206 (Evaluation of safety of veterinary vaccines and immunosera) and 2325 (Rabbit haemorrhagic disease vaccine – inactivated). The vaccine batches used in those studies have not contained the maximum antigen quantity which is acceptable according to MUMS guideline for products classified as MUMS.

Safety of the administration of one dose and the repeated dose administration of one dose studies were provided.

One dose was administered to pregnant rabbits. The repeated dose was administered to pet rabbits. Dwarf rabbits were chosen as pet since they are considered the most sensitive category due the extremely low weight and size. This approach is considered appropriate.

2.1.1. Safety in pregnant rabbits

A single dose administration study was performed in pregnant rabbits in the last third of gestation.

The number of animals involved in the study, the dose and route of administration and the observation period were in line to the Ph. Eur. monographs 04/2013:2325 (Rabbit haemorrhagic disease vaccine – inactivated) and 04/2013:50206 (Evaluation of safety of veterinary vaccines and immunosera). Pregnant animals were observed until 1 day after parturition. The animals used in the study were seronegative for RHDV and RHDV2.

On the basis of the results no safety concerns arose following the administration of one dose for vaccination to female rabbits at the last third stage of pregnancy. However, it was observed that two animals from control group (PBS group) aborted and one animal from vaccinated group. Other recorded parameters did not show significant differences between groups (rectal temperature, average litter size and general and local clinical signs). Because of this, the abortions can be considered due to the handling.

The section 4.7 (Use during pregnancy, lactation or lay) of the SPC has therefore been updated accordingly: *"Laboratory studies in doe rabbits in the last third of gestation have not produced any evidence of a teratogenic, foetotoxic and maternotoxic effects"*. Due to the sensitivity of pregnant rabbits and the possibility of abortions due to handling, a warning about this issue has also been introduced in the same section of the SPC.

2.1.2. Safety in pet (dwarf) rabbits

A safety study was provided in pet (dwarf) rabbits. A repeated dose was administered 14 days after the first vaccination. Animals were observed and examined daily. Local and general signs were observed till day 35 and rectal temperature was recorded till day 20 at regular intervals.

Adverse reactions were observed including a transient temperature increase slightly above 40 ºC and the presence of nodules or swelling (< 2 cm). Both adverse reactions resolve without need of treatment. Therefore, adverse reactions have been addressed by the safety warnings in the SPC, section 4.6

Overall, it can be concluded that the vaccination is well tolerated when performed in accordance with the SPC and pregnant does in the last third of gestation and pet rabbits can be vaccinated with ERAVAC.

2.2. Efficacy

To support the efficacy not only for fattening rabbits, an efficacy study in accordance with the current Ph. Eur. monographs and CVMP guidelines on rabbits was performed.

2.2.1. Duration of immunity (DOI)

The data submitted by the applicant as a variation has the purpose to support a 12 months DOI.

DOI of 9 months was demonstrated by means of a challenge. Sixty-nine (69) seronegative animals were used. More than 30% of the animals in the group control died. All the vaccinated animals survived. In the Ph. Eur. monograph 04/2013:2325 for the classical disease (RHDV) the survival percentage is established over 90%. Ph. Eur. monograph was taken as an appropriate guidance to assess the efficacy of the vaccine against RHDV2. It was considered acceptable if a percentage

equivalent to or higher than 87.5% of vaccinated animals show no signs of RHDV2.

The median for the ELISA titre in the vaccinated group before and after the challenge was 160 and the median of the ELISA titre in the control group was 40 after the infection.

Nevertheless, due to the failure to develop a challenge for one-year old animals, the applicant provided additional data in order to demonstrate the correlation between antibodies and protection.

Serological data showed that the antibody levels were similar nine months and one year postvaccination.

Revaccination: since rabbits were challenged 9 months after vaccination, revaccination is recommended 9 months after vaccination.

Given current knowledge about the challenge strain and its mortality rates, the CVMP considers that the mortality rate in this study in adults was consistent and the study therefore acceptable.

Overall, it can be concluded that the DOI of 9 months is justified by challenge. Vaccination induces the production of hemagglutination inhibition antibodies that persisted for at least 12 months.

3. Benefit-risk assessment of the proposed change

This product was authorised for active immunisation only of fattening rabbits from the age of 30 days to reduce mortality caused by RHDV2.

The proposed variation is to demonstrate safety in pet (dwarf) and pregnant rabbits and to amend the duration of immunity. The benefit-risk assessment below will focus only on that.

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

3.1. Benefit assessment

Direct therapeutic benefit

The therapeutic benefit of ERAVAC is its efficacy in active immunisation of rabbits to reduce mortality caused by RHDV2, considered a new variant of the rabbit haemorrhagic disease virus. The vaccine provides protection only against RHDV2, cross protection against classical RHDV is not demonstrated.

The efficacy was demonstrated in well-designed laboratory studies in rabbits.

The DOI was investigated and it can be considered that protection of rabbits at least 9 months after vaccination is achieved by the vaccine as it has been demonstrated by challenge. The presence of the antibodies at 12 months post vaccination has been included in the SPC.

Additional benefits

ERAVAC increases the range of available treatment possibilities for pregnant females and pet (dwarf) rabbits.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Administration of ERAVAC in accordance with SPC recommendations is generally well tolerated in the target animal. The main reported adverse reactions are a transient temperature increase in dwarf rabbits which resolves spontaneously without treatment and a slight swelling and nodule at the injection site, which disappears without need for treatment.

Concerns have been raised for the possibility of abortion in pregnant females and handling has been considered as the main cause of abortion. An appropriate warning has been included in the SPC.

Risk for the user:

Risk for the user remains unaffected by this variation.

Risk for the environment:

Risk for the environment remains unaffected by this variation.

Risk for the consumer:

Risk for the consumer remains unaffected by this variation.

Special risks:

No special risks of the vaccine have been identified.

3.3. Risk management or mitigation measures

Target animal safety:

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, user safety and environmental safety. The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for ERAVAC can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to amend the duration of immunity and demonstrate safety in pet (dwarf) and pregnant rabbits.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I, IIIA, IIIB.