5 December 2019
EMA/685111/2019

CVMP assessment report for grouped type II variation for Eravac (EMEA/V/C/004239/II/0005/G)

Vaccine 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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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 20 September 2019 an application for a grouped type II variation for Eravac.

1.2. Scope of the variation

Variation(s) requested		**Type**
C.I.3.z	Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done under A 45/46 - Other variation	IB
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

to extend the duration of immunity from 9 months to 12 months and to add a new sentence in section 4.6 of the SPC following the last PSUR. The MAH also takes opportunity to make complete the contact details list of local representatives.

Variation details:

Present SPC situation	**Proposed change**
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: **9 months** demonstrated by challenge **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 increase resolves spontaneously without treatment by day 5 post-vaccination. Very common: nodules or swelling (< 2 cm) can be observed in the injection site, which may last 24 hours. These local reactions gradually reduce and disappear without need for treatment.	**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: **12 months** demonstrated by challenge **4.6 Adverse reactions (frequency and seriousness)** A transient temperature increase slightly above 40 ºC might very commonly occur between two or three days following vaccination. This slight temperature increase resolves spontaneously without treatment by day 5 post-vaccination. Nodules or swelling (< 2 cm) can be very commonly observed in the injection site, which may last 24 hours. These local reactions gradually reduce and disappear without need for treatment.

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. Revaccination**: 9 months** after vaccination. Before use allow the vaccine to reach room temperature. Shake well before administration.	Lethargy and/or inappetence may be observed very rare in the first 48 hours after injection based on post-authorisation pharmacovigilance reporting. **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. Revaccination: **12 months** after vaccination. Before use allow the vaccine to reach room temperature. Shake well before administration.

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 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 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 rabbit is considered a minor species.

2. Scientific Overview

In the current variation, the MAH has applied to extend the duration of immunity from 9 months to 12 months, and to make the related changes in the SPC, which is classified as a variation type II. The duration of immunity has been assessed by means of a challenge carried out 12 months post-vaccination. The study has been performed in accordance with the current European Pharmacopoeia monographs and Guidelines.

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

2.1. Duration of immunity

The duration of immunity of Eravac against the new variant RHDV2 has been assessed in a laboratory trial.

The purpose of this study was to demonstrate experimentally the duration of immunity of Eravac against the new variant RHDV2 (challenge strain V-1035). For this reason, rabbits were vaccinated with Eravac and the efficacy of the vaccine was assessed 12 months post vaccination.

For the study, rabbits of the youngest recommended age for vaccination (1 month old) were vaccinated according to the recommended administration route (subcutaneous) and using the proposed schedule of administration (1 single dose). Rabbits seronegative to RHDV2 were used for the study. The conditions of the challenge, the route of administration, the challenge strain and the chief parameters assessed were the same as the ones used to assess the efficacy of the vaccine in the original dossier.

The animals (48 in total) were divided into two groups of 24 animals each (one control group and one vaccinated group), with the aim to conduct a challenge at 12 months post vaccination in order to assess the duration of immunity of the vaccine.

The minimum number of rabbits per group (20) was established in agreement with Ph. Eur. monograph 2325.

On D0 animals from group A were vaccinated with Eravac 0.5 ml (with strain V-1037 as active substance): ≥70% cELISA40, via subcutaneous route. At the same time, 0.5 ml of PBS was administered to animals from group B (control). Blood samples were taken from D-7 to D-1, and at D0 to ensure that all the rabbits were negative to RHDV2. Blood samples were also taken at four time points after the vaccination. On D370 all the animals were challenged, clinical signs were recorded, and deaths monitored. The RHDV2 challenge strain is the same as the one used previously by HIPRA for the efficacy studies in the original dossier.

The efficacy parameters assessed in this study were:

- Mortality: The statistical comparison between vaccinated and control animals in order to assess efficacy was conducted using Chi-square test.

- Serology: Descriptive statistics were performed, and a t-test was used to compare the antibody levels between groups.

The results obtained show that only one of the animals from the vaccinated group (A) died after challenge. However, 8 out of 23 animals of the control group died within 24 hours post challenge. No other signs of disease were reported. The control group had a mortality rate of 35% when the challenge was performed 12 months post vaccination. On the other hand, 5% mortality was reported for the vaccinated group post challenge. The difference in the mortality rate is statistically different (Chi-square test; $p < 0.05$).

The serology results obtained demonstrate that all control animals remained negative up to the moment of challenge or up to 12 months post vaccination. All the vaccinated animals seroconverted, and the median antibody titre remained unaltered until the end of the study.

It was concluded that:

- Duration of immunity has been demonstrated by challenge after 12 months post vaccination;
- Revaccination of animals 12 months after initial vaccination (as it is now proposed in section 4.9 of the SPC) is considered acceptable.

2.2 Change in the section 4.6 of the SPC

The change in the SPC, Labelling or PL is also included, intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done under A 45/46, classified as variation type IB.

In relation to the variation type IB, following assessment of the periodic safety update report for Eravac covering the period 1 April 2018 to 30 September 2018, the MAH proposed to amend section 4.6 of the SPC. This amendment was to introduce additional information on the occurrence of adverse reactions, such as lethargy and inappetence, which have been reported in post-marketing pharmacovigilance data to occur very rarely. The CVMP agreed with the addition in section 4.6 *Adverse reactions* of the SPC, but proposed the following wording according to the current guidelines on expressing frequency:

"4.6 Adverse reactions (frequency and seriousness)

Lethargy and/or inappetence may be observed very rarely in the first 48 hours after injection, based on post-authorisation pharmacovigilance reporting."

Moreover, the MAH was requested to align also the wording of the section 4.6. of the SPC with the current guidelines on expressing frequency, which was done.

3. Benefit-risk assessment of the proposed change

This product is authorised for active immunisation of rabbits from the age of 30 days to reduce mortality caused by the rabbit haemorrhagic disease type 2 virus (RHDV2).

The active substance is inactivated rabbit haemorrhagic disease type 2 virus (RHDV2), strain V-1037. The product is supplied as emulsion for injection, and a single dose (0.5 ml) is administered to rabbits from the age of 30 days as subcutaneous injection in the lateral thoracic wall. Revaccination was 9 months after vaccination and is now proposed to be 12 months after vaccination.

The withdrawal period is zero days.

The proposed variation is to extend the duration of immunity from 9 months to 12 months and to add a new sentence in section 4.6 of the SPC following the last PSUR. The MAH also took opportunity to make complete the contact details list of local representatives.

The product has been classified as MUMS/limited market and therefore reduced data requirements apply, which 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 to be a new variant of the rabbit haemorrhagic disease virus. The

vaccine provides protection only against RHDV2; cross-protection against classical RHDV is not demonstrated.

DOI study has been performed by means of a challenge and it can be considered that protection of rabbits for at least one year after vaccination is achieved by the vaccine.

Additional benefits

Eravac increases the range of available treatment possibilities for pregnant females and dwarf rabbits, which is an indication classified as MUMS/limited market. The vaccine provides a new possibility for prevention of the virus, not covered by vaccines against the "classical" RHDV.

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 rabbit haemorrhagic disease type 2 virus (RHDV2), inactivated in accordance with SPC recommendations, is generally well tolerated. The main reported adverse reactions include very commonly a transient temperature increase slightly above 40 ºC during the two or three days following vaccination, which resolves spontaneously without treatment by day 5 post vaccination. Nodules or swelling (< 2 cm) can be very commonly observed in the injection site, which may last 24 hours. These local reactions gradually reduce and disappear without need for treatment. Lethargy and/or inappetence may be observed very rarely in the first 48 hours after injection, based on post-authorisation pharmacovigilance reporting.
In addition, as a result of the variation type IB presented by the MAH, some changes in the SPC have been proposed to implement the outcome of a procedure concerning PSUR.

Risk for the user:

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

Risk for the environment:

Eravac is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk for the consumer:

Rabbit haemorrhagic disease type 2 virus (RHDV2) inactivated vaccine has been evaluated previously in respect to the safety of residues and is included in Table I of the Annex to Regulation (EU) No 37/2010 with a "no MRLs required" classification for target species and food commodities concerned under this application. Eravac is not expected to pose a risk to the consumer of meat derived from treated animals when Eravac is used according to the proposed SPC recommendations.

3.3. Risk management or mitigation measures

The withdrawal period is set at 0 days.

User safety:

User safety risks have not been identified.

Environmental safety:

No risks have been identified.

Consumer safety:

No risks have been identified.

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, environmental safety and consumer safety.

Based on the data presented, the overall benefit-risk ratio is deemed positive.

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:

C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one: Extension of the DOI from 9 months to 1 year post vaccination.

C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done under A 45/46 – Other variation.

The amended PI text presented in section 4.6 is acceptable, since it is aligned with the current guidelines on how to express frequency of adverse reactions. Therefore the CVMP considers the variation can be approved.

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

I and IIIB

Please refer to the separate product information showing the tracked changes.

As a consequence of these variations, sections 4.2, 4.6, and 4.9 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.