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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Yurvac RHD (EMEA/V/C/005992/VRA/0001)

Vaccine common name: Rabbit haemorrhagic disease and RHDV2 vaccine (recombinant)

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Laboratorios Hipra, S.A. (the applicant), submitted to the European Medicines Agency (the Agency) on 29 June 2024 an application for a variation requiring assessment for Yurvac RHD.

1.2. Scope of the variation

Variation(s) requested	
G.I.7.a	G.I.7.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one

To introduce in the product information:

- a new indication, "for passive immunisation against RHD of the offspring of the does vaccinated with Yurvac RHD vaccine."

- the required pharmacovigilance text under annex II.

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. Limited market status

Not applicable.

2. Scientific Overview

Yurvac RHD, was granted a marketing authorisation in September 2023.

The applicant proposes the following variation to introduce in the product information:

- a new indication, "for passive immunisation against RHD of the offspring of the does vaccinated with Yurvac RHD vaccine."

- the required pharmacovigilance text under annex II.

The active substance of Yurvac RHD is a recombinant RHD (rabbit haemorrhagic disease) virus capsid protein antigen (*Komagataella phaffii* as a host strain expressing rabbit haemorrhagic disease virus 2 protein VP60), which, administered to the animals, creates an active immunity against the RHD virus.

The potency is 0.7 RP (Relative Potency) per dose. The product contains light mineral oil as adjuvant which corresponds to USP (United Sates Pharmacopoeia) requirements.

It is an emulsion for injection available in glass vials of 0.5 ml (1 dose) or 5 ml (10 doses) and PET vials with 20 ml (40 doses) or 100 ml (200 doses).

During the assessment for the authorisation of the dossier, eleven laboratory trials and a field clinical trial were submitted. Onset of immunity was demonstrated for both, classical RHDV (14 days post-vaccination) and RHDV2 virus (7 days post-vaccination), including highly virulent strains. Duration of immunity was established at one year post-vaccination. The interference of MDA was also assessed and it was demonstrated that the presence of MDA did not interfere with the efficacy of the vaccine.

In this variation, the applicant has presented an additional study to support the claim for passive immunisation against RHD of the offspring of the does vaccinated with the vaccine.

The study provided to support the variation was carried out to assess the passive immunity in the progeny of does vaccinated with Yurvac RHD against RHD during pregnancy. At 30 days of age, the offsprings were challenged experimentally with a no highly virulent RHDV2 challenge strain (Strain V-1037).

There is no specific Ph. Eur monograph for RHDV2. Nevertheless, the applicant has followed the requirements described in the current monograph 2325, "Rabbit Haemorrhagic Disease Vaccine (Inactivated)" as far as possible when designing the study. Some deviations have been considered, for instance for the mortality rates obtained post-challenge.

The requirements of the current general monograph 50207 "Evaluation of efficacy of veterinary vaccines and immunosera" have also been taken into account when designing this study.

The study was carried out by using the recommended method and route of administration (subcutaneous). For the study, 15 pregnant does with different vaccination schedules were included in the study. A group of seven does (A) were vaccinated with Yurvac RHD 300 days before the beginning of the study. A second group (B) of five does were vaccinated with Yurvac RHD 84 days before the beginning of the study, and a third group (C) of three mock-vaccinated with PBS (Phosphate Buffered Saline) does were also included. All does were administered with 0.5 ml of vaccine or PBS.

From these does, a total of 25 kits from each group were selected and were distributed in three corresponding groups.

Kits were enrolled in the trial at 30 days of age (Day 0) and were challenged (RHDV2 challenge strain V-1037) by intramuscular route in order to assess the passive immunity received from the vaccinated does. The serological status of the animals was confirmed with blood samples on Day 0 prior to challenge.

The main efficacy parameter assessed in this study is mortality caused by RHDV2 virus. The proportion of animals that died per group were analyzed with a $\chi 2$ test.

A secondary parameter evaluated was the presence of typical clinical signs of RHD. The disease is characterized for causing mainly rapid mortality thus clinical signs could be less evident. Additionally, as a secondary parameter, the serological status was also evaluated. Serological response (log2 HAI/50µl Ac against RHDV2) on different days were compared between groups and analysed.

All the animals were observed daily after challenge for 14 days to check general clinical signs and mortality. Fourteen days after challenge, all rabbits were euthanized and liver samples from dead animals were analyzed to assess the presence of RHDV2, in order to confirm the cause of death.

Blood samples of does and kits at different time points along the trial were collected in order to assess the evolution of the antibodies against RHDV2. In does, blood samples were collected the day of vaccination (Day -300, Day -84) and at parturition. In kits, blood samples were collected the day of challenge (Day 0), and 14 days after challenge (D14) to assess serological response.

For the vaccine to demonstrate the efficacy of the passive immunity received by the offspring, significant differences in mortality had to be observed between kits from mock-vaccinated does and kits from vaccinated does.

The results are as follows:

The mortality rate observed after challenge in the control group C (64%) was significantly higher ($p < 0.05$) than that obtained in the vaccinated groups A and B (0% in both groups). No significant differences in mortality were observed between the vaccinated groups A and B. All deaths of the control group were reported between 24 and 48 hours after challenge. Necropsies were conducted in every death animal. No clear macroscopic lesions were observed in none of the necropsied animals. Liver samples were collected and tested for the presence of RHDV2. In the control group, all deaths were confirmed as positive to RHDV2 in liver. These results conclude that 64% of the control animals died due to RHDV2 (16/25), which was significantly ($p<0.05$) greater than the 0% obtained for the offspring from Yurvac RHD vaccinated does.

Clinical signs: No clinical signs were recorded during the challenge period.

Serology: All the does enrolled in the study were seronegative at the day of vaccination (D0).

The serological results obtained from all kits demonstrate that the offspring from vaccinated does with Yurvac RHD presented antibodies against RHDV2 before challenge, whereas all offspring from mock-vaccinated does were seronegative against RHDV2 until the challenge (day 14).

Serological titers detected in the survivors from the control group, confirms that the challenge was properly performed.

In terms of percentage of seropositive animals per group, kits from vaccinated does (groups A and B) were seropositive at the time of challenge, whereas all kits from control does remained seronegative. Fourteen days post-challenge (day 14 of the study), all the survival animals from all groups were seropositive.

After challenge, 16 out of 25 kits from non-vaccinated does group died due to RHDV2 infection. In contrast, all the rabbits from does from the vaccinated groups survived to the RHDV2 virulent challenge. Thus, passive immunity generated in kits due to vaccination with YURVAC RHD of their does, reduces the mortality in the offspring caused by RHDV2 after an experimental infection.

In relation to the mortality rate in the control group after challenge, there is a deviation in comparison with the Ph. Eur. monograph 2325 which is specific for the classical RHD ("The test is not valid if fewer than 80 per cent of control rabbits die with typical signs of RHD within 120 h of challenge."). Nevertheless, the mortality rate obtained in the control group is similar to those found in bibliography for RHDV2. Therefore, the challenge model is appropriate.

No clinical signs related to RHDV2 were detected after challenge, and sudden death was observed at 24-48h after challenge in most of the control animals. Thus, clinical signs are not considered a relevant parameter in order to assess the efficacy of the vaccine.

On the other hand, serology results show that after challenge, all survival animals were seropositive to RHDV2. These results validate that the challenge was properly performed.

In view of these results, the efficacy of the passive immunity of Yurvac RHD against RHDV2 is

demonstrated. The vaccine has been demonstrated to reduce mortality in the offspring at 30 days of age from does vaccinated from 269 days to 53 days prior to parturition by obtaining 100 % survival rates after challenge. Differences between the control and vaccinated groups were statistically significant.

Based on all the above, the CVMP concluded that passive immunisation is demonstrated. Nevertheless, the indication in the PI proposed under section 3.2 ("for passive immunisation against RHD of the offspring of the does vaccinated with Yurvac RHD vaccine") is amended in order to clarify the challenge strain used and the age at which the animals were challenged. The younger are naturally protected against the classical RHD virus.

Therefore, the sentence in section 3.2. of the SPC reflects these considerations as follows:

"For passive immunisation against RHDV2 (not demonstrated against highly virulent strains) of the offspring of the vaccinated does for at least 30 days."

In section 4.1. the following paragraph is introduced for clarification: "The vaccine is intended to stimulate active immunity against RHDV and RHDV2 and passive immunity against RHDV2. Passive immunity against highly virulent RHDV2 strain was not tested. The younger are naturally protected against the classical RHD virus."

Part 4 of the dossier (Efficacy) has been provided.

The benefit-risk balance remains unchanged.

The PI has been updated to reflect the result of this VRA.

Additionally, annex II has been updated with the following sentence:

ANNEX II

OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

SPECIFIC PHARMACOVIGILANCE REQUIREMENTS:

"The MAH shall record in the pharmacovigilance database all results and outcomes of the signal management process, including a conclusion on the benefit-risk balance, according to the following frequency: annually."

Conclusion:

The changes proposed by the MAH are acceptable.

3. Benefit-risk assessment of the proposed change

This product is authorised for the active immunisation of rabbits, including pet (dwarf) rabbits, from 30 days of age onwards to reduce mortality of rabbit haemorrhagic disease (RHD) caused by classical RHD virus (RHDV) and variant strains (RHDV2), including highly virulent strains. Each dose of 0.5 ml contains recombinant RHDV2 virus capsid protein RP*≥ 0.7 (Relative Potency (ELISA test)). It is for subcutaneous use. The withdrawal period is zero days.

The proposed variation is to introduce in the product information:

- a new indication, "for passive immunisation against RHD of the offspring of the does vaccinated with Yurvac RHD vaccine."

- the required pharmacovigilance text under Annex II.

3.1. Benefit assessment

Direct therapeutic benefit

Efficacy was established for the proposed indication: "For passive immunisation against RHDV2 (not demonstrated against highly virulent strains) of the offspring of the vaccinated does for at least 30 days."

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Safety (user, consumer, environmental, target animal) remains unaffected by this variation.

3.3. Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety, consumer safety, target animal safety.

The product has been shown to be efficacious for passive immunisation against RHD of the offspring of the does vaccinated with Yurvac RHD vaccine.

Specific pharmacovigilance requirements have been included in the SPC and other product information under Annex II.

The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original data presented on efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Yurvac RHD is approvable, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows**:**

To introduce in the product information:

- a new indication, "for passive immunisation against RHD of the offspring of the does vaccinated with Yurvac RHD vaccine."

- the required pharmacovigilance text under Annex II.

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 Union marketing authorisation.

I, II and IIIB

As a consequence of this variation, sections 3.2 of the SPC (Indications for use for each target species), section 4 (IMMUNOLOGICAL INFORMATION) and Annex II are updated. The corresponding sections of the Package Leaflet are updated accordingly.